A GUIDE ON SURGICAL INNOVATION FOR GLAUCOMA

European Glaucoma Society

Innovation, Education, Communication, Implementation

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Table of Contents

Prologue

Glaucoma surgery has been, for many decades now, dominated by the universal gold standard which is trabeculectomy augmented with antimetabolites. Tubes also came into the scene to complement what we use to call conventional or traditional glaucoma surgery. More recently we experienced a changing glaucoma surgery environment with the "advent" of what we have become used to calling Minimally Invasive Glaucoma Surgery (MIGS). What is the unmet need, what is the gap that these newcomers aim to fill?

Hippocrates taught us "bring benefit, not harm" and new glaucoma techniques and devices aim to provide safer surgery compared to conventional surgery. For the patient, but also for the clinician, safety is important. Is more safety achieved with new glaucoma surgery and, if so, is it associated with better, equivalent, or worse efficacy? Is new glaucoma surgery intended to replace conventional surgery or to complement it as an 'add-on' to what clinicians already have in their hands to manage glaucoma? Which surgery should be chosen for which patient? What are the options? Are they equivalent? These are too many questions for the clinician! What are the answers to the questions? What is the evidence to support answers? Do we need more evidence and how can we produce high-quality evidence? This EGS Guide explores the changing and challenging glaucoma surgery environment aiming to provide answers to these questions.

The EGS uses four words to highlight a continuum: Innovation, Education, Communication, and Implementation. Translating innovation to successful implementation is crucially important and requires high-quality evidence to ensure steps forward to a positive impact on health care when it comes to implementation.

The vision of EGS is to provide the best possible well-being and minimal glaucoma-induced visual disability in individuals with glaucoma within an affordable healthcare system. In this regard, assessing the changes in glaucoma surgery is a pivotal contribution to better care. As mentioned, this Guide aims to provide answers to the crucial questions above. However, every clinician is aware that answers may differ for every person: an individualised approach is needed. Therefore, there will be no uniform answer for all situations and all patients. Clinicians would need, through the clinical method and possibly some algorithm, to reach answers and decisions at the individual level. In this regard, evidence is needed to support clinicians to make decisions. Of key importance in this Guide is to provide an overview of existing evidence on

Prologue

glaucoma surgery and specifically on recent innovations and novel devices, but also to set standards in surgical design and reporting for future studies on glaucoma surgical innovation. Designing studies in surgery is particularly challenging because of many subtle variations inherent to surgery and hence multiple factors involved in the outcome, but even more because one needs to define carefully outcomes relevant to the research question but also to the future translation into clinical practice. In addition this Guide aims to provide clinical recommendations on novel procedures already in use when insufficient evidence exists.

EGS has a long tradition to provide guidance to the ophthalmic community in Europe and worldwide through the EGS Guidelines (now in their 5th Edition). The EGS leadership recognized that the changing environment in glaucoma surgery currently represents a major challenge for the clinician, needing specific guidance. Therefore, the decision was made to issue this Guide on Glaucoma Surgery in order to help clinicians to make appropriate decisions for their patients and also to provide the framework and guidance for researchers to improve the quality of evidence in future studies. Ultimately this Guide will support better Glaucoma Care in accordance with EGS's Vision and Mission.

Fotis Topouzis
EGS President

Fotis Topouzis

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All contributors have provided the appropriate COI visible in detail at www.eugs.org/pages/guidesurgical/

This manuscript reflects the work and thoughts of the list of individuals recognized above, but importantly, it reflects EGS views on the subject matter. Its strength originates from a team effort, where a cohesive group of authors and reviewers have worked towards a common goal and now stand behind the text in its entirety. The EGS nevertheless wishes to thank the following external contributors for their additional expertise, which was particularly valuable to the development of this Surgical Guide: Amanda Bicket, Jonathan Bonnar, Catey Bunce, Kuan Hu, Sheffinea Koshy, Jimmy Le, Tianjing Li, Francisco Otarola, Riaz Qureshi, Anupa Shah, Richard Stead and Marta Toth. A particular appreciation goes to Ian Saldanha for drafting the introductory overview on Core Outcomes on chapter 8. Finally, EGS would like to acknowledge Augusto Azuara Blanco, Chair of the Scientific and Guidelines Committee, for his expertise and advisory role throughout the entire process.

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1. Introduction

Glaucoma surgery is a rapidly evolving field. The number of options offered to glaucoma patients has recently expanded far beyond traditional trabeculectomy and drainage devices. MIGS (Minimally Invasive Glaucoma Surgery), a relatively recently developed group of surgical procedures, has raised substantial interest among surgeons over the past few years.
New techniques have been introduced, some of which were rapidly abandoned. Evidence has been incomplete or lagging behind the literature, being somewhat slower in providing all stakeholders with information on the clinical value of these novel procedures. Surgeons, general clinicians, patients and industry have thus been making decisions regarding the uptake of procedures based on unclear and heterogeneous factors.
Other scientific societies, such as the World Glaucoma Association - WGA, have made valuable contributions to the design and reporting of glaucoma surgical trials,1 suggesting that the development of standardised methodologies and outcomes would enhance the interpretation and transparency of study results and facilitate comparisons among reports and techniques.2 Most published MIGS trials however show low adherence to such guidelines.
To overcome this unmet need, the European Glaucoma Society (EGS) has set up a Surgical Taskforce to promote a more standardised approach to the critical area of innovative surgeries. Its aim is to create the right conditions to generate the evidence needed to inform best surgical practice.
This Guide for glaucoma surgery was developed with three main goals::

I. To provide the ophthalmology community with an overview of the existing evidence on novel devices.
II. To provide clinical recommendations on novel procedures already used in clinical practice but where evidence was found to be insufficient.
III. To harmonise common standards in surgical trial design and reporting, providing guidance and facilitating the implementation of future studies on glaucoma surgical innovation.

These three pillars aim to provide a continuum, presenting information to a wide audience, ranging from the general ophthalmologist to the glaucoma specialist.
While this Guide concerns technologies available at the time of writing, the concepts and methodologies described will hopefully apply to future surgical innovations.
The definitions section aims to provide a summary description of the data on the recently introduced devices, covering their mechanism of action and the overall concept of their relative efficacy and safety.
One section is dedicated to a literature review.
TThe clinical recommendations section aims to provide clinical guidance on topics relevant to the surgeon interested in novel techniques. Practical questions were identified by a European-wide survey and addressed using a consensus approach to help decision-making in areas where there is currently insufficient evidence. There is also a focus on techniques where group experiences rather than individual experiences guide the discussion. This is intended to offer guidance for interventions that are popular enough to be widely used while avoiding bias toward techniques which currently are niche techniques. In continuity with the previous EGS work on providing clinically oriented guidance, a “choosing wisely” list is also suggested.
The purpose of the section on clinical trials design is to propose ways to improve the quality of designing trials for surgical innovation. This approach builds on a long-lasting effort by

scientific societies to promote quality evidence in the field of surgery. The challenges posed by innovative surgeries triggered within the EGS a healthy debate that led to the present Guide. A central aspect is to promote the reporting of core outcomes as part of an effort to allow proper benchmarking. Only by reporting the same outcomes in a similar fashion will we be able to compare techniques.

This work was also considered an opportunity offered not only to the promoters of surgical trials, investigator-led or otherwise, but to the general audience on how to interpret the findings. Accordingly, an overview of items covering study designs, strengths, caveats, complications and data collection methods is provided. To maximise implementation, EGS developed a sample case-report form (CRF) to facilitate data collection.

This team effort resulted in a broad consensus across a range of experienced European surgeons and glaucoma specialists. Having a group of experts brings two main advantages: 1) it follows the EGS "spirit" of enriching the group through a variety of experience, and 2) it minimises bias towards any specific surgical innovation.

At the time of the consensus meetings, experience with some emerging technologies had not matured enough to provide recommendations. For this reason, some novel devices are not covered in the clinical guidance section.

Finally, this Guide has been externally reviewed by third parties, namely our partner external Glaucoma Societies (MEAGS, AGS, APGS and WGA) who have enriched our work with their insights and resonance with their members. The link to their reviews can be found www.eugs.org/pages/externalreviewers.

2. Definitions and surgical technical overview

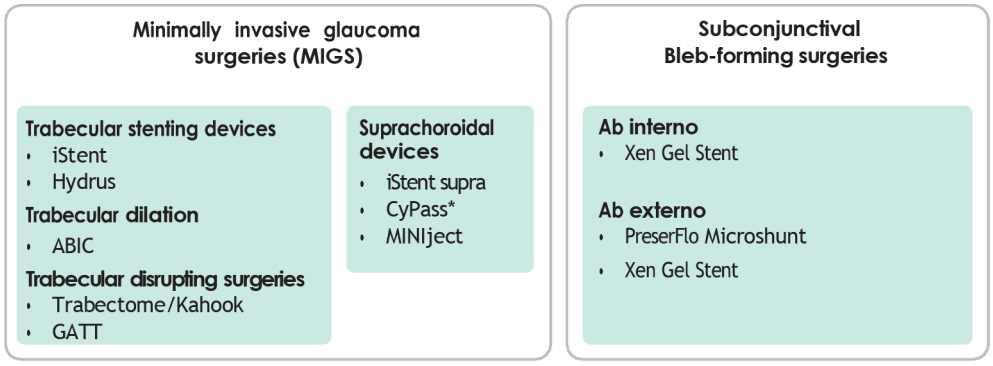
In the past decade, surgical innovation has followed two different approaches. We distinguish between:

A. MIGS "Minimally Invasive Glaucoma Surgery", defined by the 5th Ed. EGS Guidelines3 as ab-interno, non-bleb forming procedures;

B. "Subconjunctival bleb-forming surgery" including devices used either ab-interno or ab externo (Diagram 1).

The scope of this chapter is to provide the reader with an overview of the techniques for which sufficient evidence was available at the time of writing.

Diagram 1. List of procedures included in this Guide



MIGS: Minimally invasive glaucoma surgery
GATT: Gonioscopy assisted transluminal trabeculotomy
ABIC: Ab interno canaloplasty
*Cypass-MS has been withdrawn from the market

The European Glaucoma Society Guidelines define as MIGS only the ab-interno non-bleb-forming procedures

2.1 Minimally Invasive Glaucoma Surgery (MIGS)

MIGS, a group of surgical procedures relatively recently developed, has attracted substantial interest among surgeons in recent years. Numerous authors have claimed the merits of MIGS because of good safety profile, rapid recovery and user-friendly potential.[4,5]

Theoretically, such features would allow for new paradigms in glaucoma surgery, such as a shift in decision-making towards intervention at an earlier stage of the disease and an individual approach adapted to the needs of each patient, accounting for the variability of the risk profile such as age, stage of disease, rate of progression, anatomy and comorbidities.[6]
The number of MIGS procedures is growing continuously, and their use is becoming widespread among cataract surgeons and glaucoma specialists.
In theory, MIGS should only minimally alter the essential anatomy or physiology of the eye and feature both safety and fast recovery. This new tissue-sparing approach has stimulated ophthalmologists to consider surgery earlier in the management algorithm and for reasons parallel to intraocular pressure (IOP) lowering, such as reducing medication burden and improving patient comfort and vision-related quality of life. However, the IOP-lowering effect of these procedures is inferior to filtration surgery.
MIGS can be classified as trabecular procedures/devices and supra-choroidal devices.

2.1.1 Trabecular procedures and devices

Devices targeting Schlemm's canal (SC) through the trabecular meshwork (TM) are divided into stenting and disrupting procedures.
Their use implies proficiency with intraoperative gonioscopy and requires repositioning of patient and microscope. Contraindications for trabecular procedures include angle closure, previous trauma, discernible congenital anomalies of the anterior chamber angle and elevated episcleral venous pressure.

2.1.1.1 Stenting procedures:

In stenting procedures, the outflow is increased by bypassing the trabecular meshwork, directing aqueous humour into the SC.
The iStent® (Glaukos Corporation, Laguna Hills, CA, USA) was the first ab-interno glaucoma implant, approved in 2012 for the management of mild-to-moderate open-angle glaucoma (OAG) in conjunction with cataract surgery.[7] The first-generation device comprised a heparin-coated, nonferromagnetic, L-shaped titanium stent preloaded in an inserter. The second and third-generation of iStents (iStent inject® and iStent W®) are smaller and conical-shaped and administered using an injector that can deliver up to two devices into the SC.
The Hydrus® microstent (Alcon Laboratories Inc., Fort Worth, TX, USA) is a crescent-shaped open structure with a curved scaffold design to match the curvature of the SC. It is made of nitinol, a nickel-titanium alloy, and is inserted via a clear corneal incision using a preloaded injector. The stent is inserted into the SC after pre-incision of the trabecular meshwork and dilates the SC for 3 clock hours, with the hope of connecting to multiple collector channels.

2.1.1.2 Dilating procedures:

The ab-interno canaloplasty is offered as ABiC™ (Ellex Medical, Adelaide, Australia). After pre-incision of the TM, a catheter with an illuminated tip is introduced into the SC, which is then cannulated over 360°. Once the distal tip has circled till the entrance site, the cannula is retrieved slowly while injecting high molecular weight viscoelastic every two clock hours. The OMNI® Surgical System (Sight Sciences, Menlo Park, CA, USA) provides a similar procedure.

2.1.1.3 Disrupting procedures

These ab-interno techniques ablate the trabecular meshwork to allow the AH to directly reach the SC.

The Trabectome® (Neomedix, Tustin, CA, USA) is used to perform trabeculotomy under intraoperative gonioscopy. A disposable handpiece with an insulated footplate with electro-cautery, irrigation, and aspiration functions is inserted into the anterior chamber and then pushed through the TM into the SC, treating 60°–120° of the nasal angle.

The Kahook Dual Blade® (KDB, New World Medical, Rancho Cucamonga, CA, USA) is a trabeculotomy procedure performed with a cutting, nonthermal instrument.[8]

Gonioscopy-assisted transluminal trabeculotomy (GATT) is a modification of the 360° suture ab-externo trabeculotomy technique. In GATT, an illuminated microcatheter is inserted into the SC via a pre-incision of the SC. The catheter is advanced circumferentially for 360°; once the distal tip of the catheter reaches the initial incision, the distal end is retrieved and pulled through the TM, thus creating a circumferential trabeculotomy.[9]

A similar technique that does not require a specific catether has also been proposed, referred to as “Prolene GATT”.[10]

2.1.2 Suprachoroidal devices

Suprachoroidal devices aim to create a controlled cyclodialysis and improve uveoscleral outflow through a connection between the anterior chamber and the suprachoroidal space. The CyPass® (Alcon Laboratories, Inc., Ft. Worth, TX, USA) is a 6.35 mm polyamide implant introduced into the supraciliary space with an ab-interno approach. CyPass® was voluntarily withdrawn from the market by the manufacturer in August 2018 due to safety issues (www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/alcon-announces-voluntary-global-market-withdrawal-cypass-micro-stent-surgical-glaucoma). The reason for withdrawal was a late endothelial cell loss 48 months after surgery, possibly related to the position of the implant.

The MiniJect® (iSTAR Medical SA, Wavre, Belgium) and other devices have been proposed as implants to be positioned in the supraciliary space with an ab-interno approach. Although clinically in use, data remain scarce at the time of this publication, and clinical trials are ongoing.

2.2 Bleb-forming devices

Subconjunctival devices create an alternative outflow pathway of aqueous humour to the subconjunctival space, similar to trabeculectomy. They follow Poiseuille's law, where the length and inner diameter of the tube influences the flow rate, theoretically limiting postoperative hypotony while obtaining a significant IOP decrease.[11] The creation of a filtering bleb however is best followed postoperatively by an ophthalmologist with experience in bleb management. Because these procedures require conjunctival manipulation and the use of cytotoxic agents such as 5-fluorouracil (5-FU) or Mitomycin C (MMC), they should not be labelled as "minimally invasive" procedures.

Cytotoxic agents are used off-label in filtering surgery; their efficacy to inhibit scarring resulting in lower IOP has been shown in systematic reviews.

The Xen® gel stent (AbbVie, Chicago, IL, USA) is a hydrophilic tube available in two lumen diameters (45 and 63 µm). It is made of porcine gelatine crosslinked with glutaraldehyde. As in other filtering procedures, MMC is recommended and is injected under the conjunctiva prior to surgery; the commonly used dose is 10-40 µg. The Xen® is approved for ab-interno implantation via a clear corneal incision. Recently, an off-labeled ab externo approach has been described for unusual circumstances.

The PreserFlo®, previously known as the InnFocus microshunt (Santen Pharmaceutical Company Ltd, Osaka, Japan), is an ab-externo drainage device made from poly-(styrene-block-isobutylene-block-styrene). It is implanted through a scleral mini tunnel after fashioning a fornix-based conjunctival bleb and application of MMC.

3. Literature review and recommendations

3.1 Methodology

The short- and long-term effectiveness, safety and efficacy of new surgical techniques should be assessed before gaining widespread use.
Here, recommendations based on consensus and current evidence for the clinical application of the techniques described in Chapter 2 are reported together with the knowledge gaps that were identified.

3.1.1 Identification of key clinical questions

Convenience sampling based on geographical representation among EGS members was carried out (see Chapter 3.4).

3.1.2 Summarizing available evidence

The Search Strategy consisted of a literature review to provide answers to the questions listed in Chapter 3.4. Specifically, data from randomized controlled trials (RCTs) and systematic reviews of MIGS were identified and summarized.[12,13]
All glaucoma surgical innovations were targeted in the search strategy, including trabecular bypass with microstents, ab-interno stenting or disrupting the trabecular meshwork, suprachoroidal devices and subconjunctival bleb-forming drainage devices.
In terms of population characteristics, eligible studies enrolled patients with primary or secondary OAG and patients with ocular hypertension (OHT).
Interventions could be associated or not associated with cataract surgery. All available comparators were accepted, including cataract extraction alone, other novel glaucoma surgeries, trabeculectomy, laser trabeculoplasty and medical therapy.
In the majority of included publications the primary outcome was the proportion of subjects not using IOP-lowering drops; this specific outcome is not endorsed by the EGS Guidelines. Secondary outcomes were the mean change in IOP, the mean change in the number of IOP-lowering drops, the proportion of participants requiring additional glaucoma procedures, intra- or postoperative complications, and health-related quality of life measures (HRQoL). Outcomes were analysed, when available, at short-term (<6 months), medium-term (6 to 18 months), long-term (>18 to 36 months), and beyond 36 months of follow-up.

3.1.3 Study selection

We consulted an overview and network meta-analysis of six Cochrane systematic reviews published between December 2018 and February 2021.[12]
Fourteen non-Cochrane systematic reviews addressing MIGS were identified (see Table 5). We classified a systematic review as "reliable" if it met the following methodological criteria: (1) defined eligibility criteria for selection of individual studies, (2) conducted a comprehensive literature search for eligible studies, (3) assessed the risk of bias of the individual included studies using any method, (4) used appropriate methods for meta-analyses (criterion only assessed if a meta-analysis was performed), and (5) we observed concordance between the review's findings and conclusions. We considered a systematic review "unreliable" when one or more of these criteria were not met.[13] The majority were methodologically flawed. Six non-Cochrane systematic reviews were methodologically acceptable and therefore added.

3.1.4 Data synthesis

Quantitative results were summarised from the systematic reviews, and a narrative description of all relevant comparisons was made, grouped by the type of MIGS procedure. In the overview of Cochrane reviews,[12] some data were meta-analysed, and summary estimates were reported along with confidence intervals and measures of statistical heterogeneity; trial-level estimates were reported when the data were not meta-analysed. Random effects network meta-analyses (NMAs) were used for outcomes examined by two or more comparisons across the included Cochrane Reviews (proportion of participants without medication, mean change in unmedicated IOP, and mean change in the number of IOP-lowering drops) at the longest follow-up analysis. NMA is an extension of standard pairwise meta-analysis and enables the simultaneous comparison of multiple interventions. A common network-specific heterogeneity parameter for each outcome and equal effects by phacoemulsification when combined with any MIGS were assumed. Summary estimates with their 95% confidence and prediction intervals in interval plots are presented.
The mean rank for each intervention was estimated per outcome. Additional RCTs not included in the systematic reviews were identified, and their quality was assessed. Data were extracted and validated by two independent investigators.
Regarding subconjunctival bleb-forming devices, a recently published large RCT compared PreserFlo® microshunt with trabeculectomy outcomes.[14] This trial had a high risk of bias: investigators were not masked, and a large number of post hoc statistical analyses, which were reported. The literature review results were summarised, and a narrative description of all relevant comparisons was provided, grouped by type of procedure.

Following the evidence synthesis, two face-to-face meetings were conducted in 2021 with the EGS Surgery Task Force. The scope of such meetings was to answer the preset key clinical questions identified by an EGS members' survey to review the evidence gathered before the meetings and to formulate recommendations to fill the knowledge gaps. No recommendations were made for procedures where the majority of the group lacked expertise. Following GRADE methodology (Grading of Recommendations, Assessment, Development, and Evaluations),[15] a tool for developing and presenting summaries of evidence that provides a systematic approach for making clinical practice recommendations, evidence to support each recommendation was classified as 'high', 'moderate', 'low' or 'very low'. Recommendations were classified as 'strong', where clinicians agreed that patients should be offered the intervention as the benefits clearly outweighed the risks, or 'weak' where the balance of benefit and risk was unclear, and the intervention would be considered optional (Tables 1-3). Furthermore, there was an expert consensus to compile a "choosing wisely" list, which is reported in Chapter 3.3.

3.2 Summary of current evidence and clinical interpretation

3.2.1 Trabecular stenting devices

This analysis is limited to two devices: iStent® and Hydrus®.[12]

Results from studies having as primary outcome measure the proportion of patients without medication:

- **Direct comparisons (i.e., comparisons made in RCTs)12 Hydrus® or iStent® compared with cataract extraction alone.** The addition of trabecular bypass with either Hydrus® or iStent® increased the likelihood of study participants remaining drop-free at the medium- term follow-up (relative risk (RR) 1.6, 95% CI 1.4 to 1.8; RR 1.4, 95% CI 1.2 to 1.6, respectively; each estimate based on 2 trials), although the certainty of the evidence was moderate for the Hydrus® comparison and very low for the iStent® comparison. For participants receiving a Hydrus®, this effect was sustained at the long-term follow-up (2 years) (RR 1.6, 95% CI 1.4 to 1.9); long-term follow-up data were unavailable for other techniques.
- **Directly comparing Hydrus® and iStent®, implanted without cataract extraction.** Study participants who received a Hydrus® were more likely to be drop-free at the medium-term follow-up than those who received an iStent® (RR 1.9, 95% CI 1.2 to 3.1). The certainty of this evidence was low, arising from only a single RCT.

- **Comparing one versus multiple stand-alone iStent®.** The additional device did not increase the proportion of participants who remained drop-free.
- **Network meta-analysis**

The NMA indicated that drop-free disease control was less likely for patients after iStent® than Hydrus® (RR 0.8, 95% CI 0.6 to 0.9, 95% PI 0.6 to 1.1).

Results from studies having the following secondary outcomes:

Mean change in IOP

- **Compared with cataract extraction alone**, moderate certainty evidence showed that adding Hydrus® lowered the IOP by 2.0 additional mmHg at the long-term follow-up (95% CI -2.7 to -1.3 mmHg; estimate based on two trials). Very low-certainty evidence suggested that adding iStent® to cataract extraction lowered the IOP an additional 5.0 mmHg (95% CI -7.5 to -2.5 mmHg; estimate based 3 trials) at the short-term follow-up, the difference was not statistically significant at the medium-term follow-up.
- **Directly comparing Hydrus® and iStent®, without cataract extraction**, moderate evidence showed that Hydrus® lowered IOP 3.1 mmHg more than iStent® alone (95% CI 2.0 to 4.2 mmHg; based on 1 trial). NMA evidence suggested a statistically significant but more attenuated effect (1.9 mmHg, 95% CI 0.3 to 3.6, 95% PI to -1.9 to 5.8).
- Neither two iStent® nor a stand-alone iStent® lowered IOP more than medical therapy at the medium-term follow-up, and while two or three iStent® showed an IOP-lowering benefit over one at the medium-term follow-up, no difference was found at either the short- or long-term follow-ups.

Mean change in IOP-lowering drops taken per day

Not all reviews contained sufficient data to describe changes in the number of IOP- lowering drops required per day, and the certainty of the evidence was low or very low in all cases.

- Hydrus®. Compared with cataract extraction alone, a combination of Hydrus® and cataract extraction reduced the daily drops required by participants by 0.41 (95% CI -0.6 to -0.3; estimate based on 2 trials) at the long-term follow-up.
- iStent®. A combination of iStent® and cataract extraction reduced the daily drops by 0.42 (range -0.6 to -0.2; based on 3 trials) at the medium-term follow-up compared with cataract surgery alone.
- Comparing Hydrus® and iStent®. Implanted without cataract extraction, Hydrus® reduced participants' daily requirement by an additional 0.6 drops (95% CI -1.0 to -0.2; estimate based on 1 trial) at the medium-term follow-up. Again, NMA evidence attenuated the size of this effect but not its direction (0.2 drops, 95% CI -0.1 to 0.6, 95% PI -0.5 to 0.9).

Proportion of participants experiencing intra- or postoperative complications

The most prevalent severe complication reported was the loss of two or more lines of vision.

- Hydrus®. Comparing cataract extraction alone to cataract surgery combined with Hydrus® implantation, available weak evidence did not indicate a definite safety difference, as most 95% CIs included the null value. For combined surgery, the RR of two or more lines of vision at long-term follow-up was 0.5 (95% CI 0.1 to 1.5), the RR of an IOP spike over 10 mmHg was 0.4 (95% CI 0.1 to 1.2), and the RR of postoperative hyphema was 1.0 (95% CI 0.1 to 11.1).
- - iStent®. Comparing cataract extraction alone with cataract surgery combined with iStent® implantation, those who underwent combined surgery were less likely to experience an IOP spike exceeding 10 mmHg (RR 0.2, 95% CI 0.1 to 0.7); however, this estimate was based on just one participant in each group.

Of note, the long-term outcomes in one study comparing Hydrus® associated with cataract surgery with cataract surgery alone have been reported, describing a greater reduction of IOP (29.5% vs 33.8% of eyes with IOP of 18 mmHg or less without medications), reduced need of medications (66% vs 46% medication free) and less frequent glaucoma surgery (2.4% vs 6.2%) after 5-year follow-up compared with cataract surgery alone.[16] A post hoc analysis also showed less visual field progression associated with Hydrus® stent (mean rate of progression –0.26 dB/y vs –0.49 dB/y for Hydrus®-phaco vs phaco alone).[17]

Conclusions on current evidence in the literature

- Hydrus® combined with phacoemulsification is probably more efficacious than one iStent® combined with phacoemulsification in terms of IOP-lowering and medication reduction
- The evidence is low for stand-alone procedures i.e., not associated with phacoemulsification

Clinical interpretation

Although Hydrus®, and iStent® can decrease the medication burden, their long-term IOP-lowering effect is relatively modest. These devices are mostly used in combination with phacoemulsification in patients requiring cataract surgery. Hydrus® and iStent® are not recommended for patients with advanced glaucoma with uncontrolled IOP or those with progressive disease (see Table 1). The surgical safety profile is good; however, further evidence on long-term outcomes is needed.

Table 1. Statements on trabecular implants (iStent® and Hydrus®)

Statements
Expected surgical outcome is a reduced drop burden*
Not intended for progressing patients or those with advanced glaucoma
Mostly used in combined procedures for patients requiring cataract surgery
Standalone use may be considered in "special circumstances" like ocular surface disease, quality of life, adherence issues
Surgical safety is good
Long-term outcomes largely unknown

** The EGS Guidelines 5th Ed. state: "the aim of decreasing medication burden as reported in some studies, rather than absolute IOP-lowering, is not in line with the traditional aim of glaucoma surgery."*

3.2.2 Trabecular procedures

Trabectome®, Kahook Dual Blade® (KDB) and catheter-assisted surgeries (GATT and ABiC™) are discussed.
The evidence available in the literature is limited.

Results from studies having as primary outcome measure the proportion of patients without medication:
Direct comparisons (i.e., comparisons made in RCTs).[12] Ab-Interno trabeculotomy with Trabectome combined with cataract extraction did not result in a greater proportion of drop-free participants than combined trabeculectomy and cataract extraction at the medium-term follow-up.

Consensus Notes

There was too little experience among participants to reach a consensus and inform practice.

Clinical Interpretation

The consensus panel agreed that there were insufficient data to provide clinical recommendations regarding these techniques. Substantial uncertainty remains regarding the efficacy and safety since the published evidence is sparse.

3.2.3 Suprachoroidal devices

Results from studies having as primary outcome measure the proportion of patients without medication:

Direct comparisons (i.e., comparisons made in RCTs).[12]

- Cypass® was withdrawn from the market in 2018. However, at the time, the existing data showed moderate certainty evidence that the addition of Cypass® to cataract surgery increased the likelihood of remaining drop-free at the medium-term follow-up (RR 1.3, 95% CI 1.1 to 1.5; estimate based on 1 trial).
- Network analysis: An indirect comparison of Cypass® with iStent® via NMA suggested that Cypass® was as likely as iStent® to render patients drop-free (RR 1.0, 95% CI 0.8 to 1.3, 95% PI 0.7 to 1.4).

Results from studies having the following secondary outcomes:

Mean change in IOP

- Adding Cypass® to cataract surgery lowered the IOP an additional 2.3 mmHg at the medium-term follow-up (95% CI -3.0 to -1.6 mmHg; estimate based on 1 trial), and the certainty of this evidence was high.
- NMA indicated similar IOP-lowering by Cypass® and Hydrus®.

Mean change in IOP-lowering drops

- Cypass®: A change of -1.2 drops after combined cataract extraction with Cypass® versus -0.7 drops after cataract extraction alone was reported.[18]

Proportion of participants experiencing intra- or postoperative complications

- Cypass®: High-certainty evidence demonstrated that the addition of Cypass® to cataract surgery increased the incidence of more than 2 lines of vision loss both at the medium- term (11 per 1000 versus 0 per 1000; estimate based on) and long-term follow-up (112 per 1000 versus 60 per 1000; estimate based on), although relative effects were not analysed. High-certainty evidence from both COMPASS XT and the FDA-mandated safety study, NCT03273907, demonstrated that the addition of Cypass® to cataract surgery increased the incidence of two or more lines of

vision loss at the medium- and long-term follow-up periods due to endothelial cell density reduction >30% in 27.2% of participants.

Consensus Notes

Moderate IOP-lowering efficacy was observed after the Cypass® stand-alone procedure or in combination with phacoemulsification.

Clinical Recommendation

Cypass® was withdrawn from the market because of long-term safety issues. Novel devices are still in the early stages of development.

3.2.4 Bleb-forming devices

This analysis focuses on PreserFlo® microshunt and Xen 45® gel stent.[14,19]

Results when primary outcome measure is the proportion of patients without medication:

Direct comparisons (i.e., comparisons made in RCTs).[14,19]

- In the comparison of the PreserFlo® microshunt with trabeculectomy: at 1 year, 71.6% vs. 84.8% of patients were medication free, respectively. The authors did not report whether this difference was statistically significant.
- In the comparison of the Xen 45® gel stent comparison with trabeculectomy at 1 year, 61.2% vs 70.5% were medication free respectively. Also here, the authors did not report if the difference was statistically significant.

Results from studies having the following secondary outcomes:

Mean change in IOP

- PreserFlo® vs. trabeculectomy mean IOP ± SD at year 1: in the PreserFlo® microshunt group, mean IOP ± SD decreased from 21.1±4.9 mmHg at baseline to 14.3±4.3 mmHg (–29.1%; P<0.01). In the trabeculectomy group, the mean IOP decreased f rom 21.1±5. 0 mm Hg to 11.1±4. 3 mm Hg (– 45.4%; P<0. 01). The success rate at one year was lower in the Preserflo® microshunt group than in the trabeculectomy group (53.9% versus 72.7%, respectively; P<0.01).

- Xen 45® vs trabeculectomy mean IOP at year 1: in the Xen 45® group, mean IOP± SD decreased from 23.1±5.8 mmHg at baseline to 14.4±4.1 (P<0.001). In the trabeculectomy group, the mean IOP decreased from 22.6±5.7mmHg to 11.8±3.5mmHg (P<0.001). The complete and qualified success rates at one year were 44.2% and 62.1% in the Xen 45® gel stent arm, compared with 59.1% and 72.7% in the trabeculectomy arm, respectively, without statistically significant differences between treatments (p≥0.144 for both success rates).

Of note, the criteria for success was not the same for these two RCTs.

Mean change in IOP-lowering drops taken per day

- PreserFlo®: at one year, in the PreserFlo® microshunt group a mean of 0.6±1.1 glaucoma medications (baseline 3.1±1.0; P<0.01) was observed; in the trabeculectomy group, the mean was 0.3±0.9 glaucoma medications (baseline 3.0±0.9; P<0.01).
- Xen 45®: mean number of topical IOP-lowering medications decreased from 2.8 at baseline to 0.6 at 12 months in the Xen arm, and from 2.5 to 0.3 in the trabeculectomy arm. The reduction in medications was statistically significant in both arms.

Proportion of participants experiencing intra- or postoperative complications

- Vision-threatening complications were uncommon and reported in 1.0% of the PreserFlo® microshunt group versus 0.8% of the trabeculectomy group. Hypotony requiring intervention was reported in 2.0% (8/395) of patients in the PreserFlo® microshunt group and 7.6% (10/131) in the trabeculectomy group.
- Surgical complications were reported in 2 (2.1%) eyes in the gel stent arm and in 3 (6.8%) eyes in the trabeculectomy arm. Clinical hypotony was 22.7% in the trabeculectomy arm vs 1.1% in the gel stent arm. The Xen 45 arm experienced 23.2% needling procedures vs 18.2% in the trabeculectomy arm. After excluding laser suture lysis from the analysis, the proportion of eyes that required postoperative intervention was lower in the Xen arm (34.7%) than the trabeculectomy arm (40.9%) P=0.024.

3.2.5 Results from comparison studies and Consensus notes

<u>Comparison of current bleb-forming devices versus trabeculectomy:</u>

High-quality literature on bleb-forming devices is scarce. One RCT was found for PreserFlo vs. trabeculectomy.14 and one RCT was for Xen 45® vs trabeculectomy.[19]

The clinical recommendations were made solely based on the clinical experience of the panel. As no head-to-head comparison between PreserFlo® and Xen 45® was available, our comments regarding the perceived efficacy, safety, technical difficulties and complications of these two devices are based upon expert opinions (Table 2).

Table 2. Considerations on comparing bleb-forming procedures with trabeculectomy

Considerations on bleb-forming vs. trabeculectomy	Strength of recommendation
Consider a higher concentration of MMC in PreserFlo® when compared to standard trabeculectomy	Weak
Consider a lower concentration of injected MMC in Xen 45® compared to standard trabeculectomy	Weak
Use the same strategy as that for trabeculectomy in terms of topical steroid	Strong
Be aware of the risk of potentially serious complications with any bleb-forming procedure	N/A
Be aware that long-term data is only available for trabeculectomy	N/A

Comparison between bleb-forming devices:
No high-quality studies directly compare the two commercially available 'plateless' bleb-forming devices (PreserFlo® microshunt and Xen 45®). Although both devices aim to lower IOP by diverting aqueous from the anterior chamber to the subconjunctival/sub-Tenon's space, there are major differences in device material, dimensions, and insertion methods likely related to differences in safety, efficacy and technical difficulty.

3.2.5.1 Results from the consensus meeting

A consensus meeting explored the perceptions of glaucoma surgeons experienced with both devices which were collected by anonymized voting for each of the following topics:

3.2.5.1.1 Efficacy

Overall, the PreserFlo® microshunt was perceived to have higher efficacy than Xen 45®. Panelists were asked to rate the efficacy profile in eyes with no previous conjunctival surgery (not high-risk eyes) from 1 to 10, with 1 indicating very poor efficacy and 10 indicating very good efficacy. The mean score for Xen 45® was 4.7, whereas that for the PreserFlo® microshunt was 7.1 (Figure 1). The lowest score given for PreserFlo® by an individual surgeon was 6, whereas that for Xen 45® was 2.

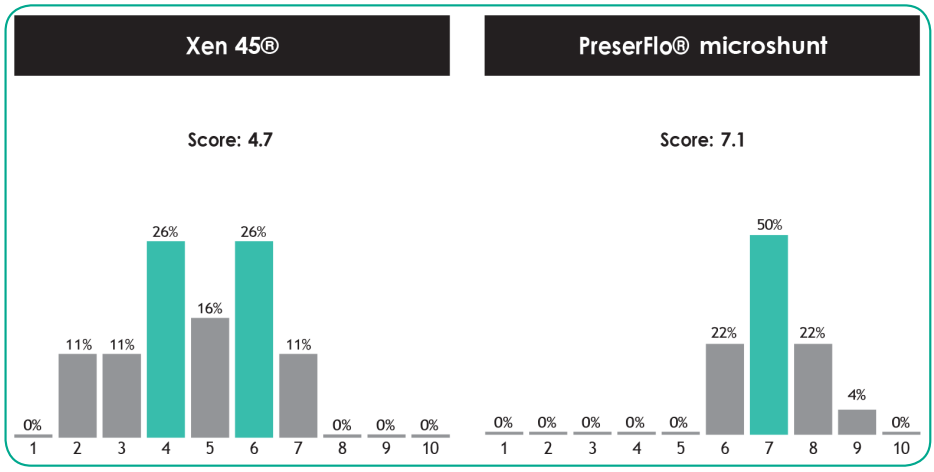


Figure 1 *Perceived efficacy among glaucoma surgeons of Xen 45® and PreserFlo® microshunt. 1 means little efficacy, 10 means highest IOP lowering efficacy.*

3.2.5.1.2 Safety

When asked to rank the safety of procedures from 1 to 10, with 1 indicating very safe and 10 very unsafe, the mean score was 3.9 for Xen 45® and 4.0 for PreserFlo® (Figure 2). The range of responses was wide; however, the consensus was that Xen 45® was safer than PreserFlo®, primarily due to a perceived lower risk of hypotony.

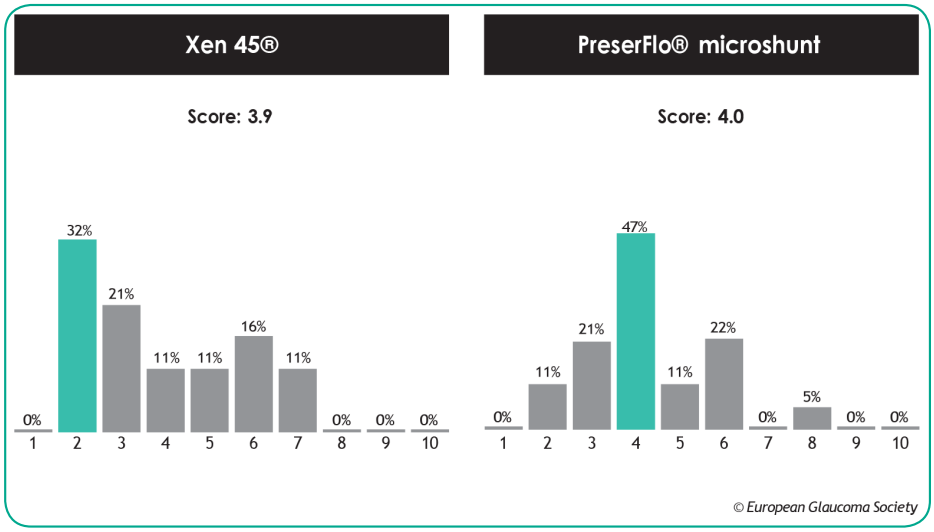


Figure 2 *Ratings of perceived safety for Xen 45® and PreserFlo® microshunt. 1 means highest safety, 10 means lowest safety.*

3.2.5.1.3 Technical difficulty

Panelists were asked to rate the difficulty of performing either procedure from 1 to 10, with 1 indicating very easy and 10 indicating very difficult. The mean score for PreserFlo® microshunt was 5.1, whereas that for Xen 45® was 5.7 (Figure 3). While the numerical mean is similar, the spread in the perceived level of difficulty was greater for Xen 45® than PreserFlo®.

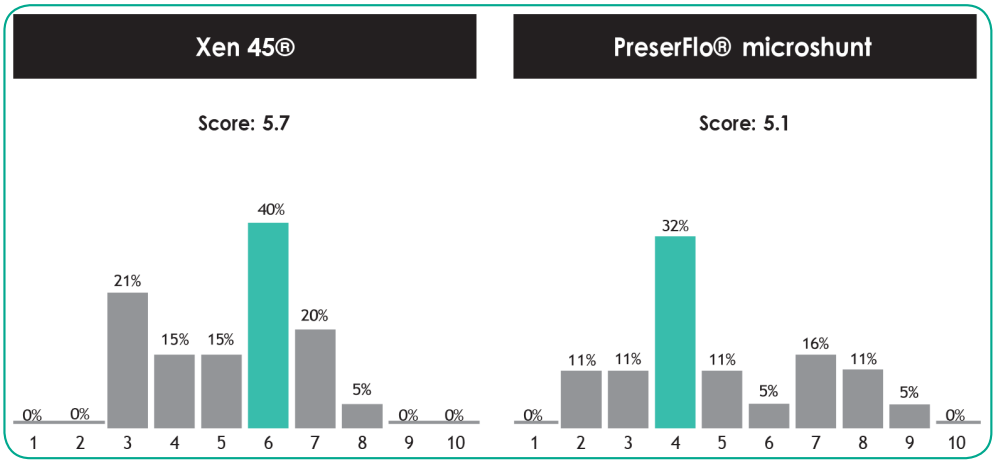


Figure 3 *Ratings of technical difficulty for Xen 45® andPreserFlo® microshunt. 1 means very little difficulty, 10 means highest complexity.*

The consensus was that the PreserFlo® microshunt has a shorter learning curve than Xen 45® if the surgeon is already experienced in filtration surgery. The panelists participating to the EGS consensus meeting were all experienced in trabeculectomy surgery, which may have influenced the perceived ease of use of the PreserFlo® microshunt, technically more similar to trabeculectomy than ab-interno Xen 45® surgery. However, Xen 45® was felt easier to perform than trabeculectomy, by 90% of participants; 5% viewed it as more difficult and 5% as similarly difficult.

3.2.5.1.4 Surgical procedure and postoperative treatment

The EGS consensus panelists strongly recommended that mitomycin C be used intraoperatively for both procedures. Without MMC, subconjunctival microshunts have a high risk of failure. A higher dose of MMC may be needed for PreserFlo® microshunt compared to trabeculectomy (weak recommendation). Regarding Xen 45®, a lower concentration of MMC was recommended for subconjunctival injection (weak recommendation). It was recommended to use the same strategy for anti-fibrotic agents (i.e. MMC) and postoperative steroids as used for trabeculectomy surgery (strong recommendation).

3.2.5.1.5 Complications

The Xen 45® was felt to be safer than PreserFlo®, primarily due to a perceived lower risk of hypotony. Regarding technical difficulties, both devices were ranked similarly. Potentially serious complications can occur with any bleb-forming procedure, including the vision-threatening complications of hypotony, bleb-related infection and device exposure (strong recommendation). Caution is warranted since the long-term safety of these devices remains uncertain (strong recommendation).

Clinical interpretation

The IOP-lowering effect of these bleb-forming devices is significant, although perceived less effective than trabeculectomy.
Postoperative bleb management is necessary and bleb revision is not uncommon.

Table 3 Considerations for bleb-forming procedures

Considerations for bleb-forming procedures:	Strength of recommendation
MMC should always be used in primary subconjunctival bleb-forming devices	Strong
When offering surgery to patients, inform them that bleb manipulations are required in a significant proportion of cases and carry a risk	Strong
Avoid repeating revisions and needlings	Strong
Consider open bleb revisions rather than repeated needlings	Strong
Anti-fibrotic agents should be used in case of both bleb needling and bleb revision (more commonly MMC than 5-FU)	Strong
Consider trabeculectomy if the primary “rescue” procedure was unsuccessful	Strong

3.2.6 Phacoemulsification

When the patient has coexistent glaucoma and cataract, a personalized approach should be taken. There was limited consensus on a generalized approach for these patients and no strong recommendation could be made. The main criteria to consider when performing combined or staged procedures should include the severity of the disease (mild, moderate or advanced) and the preoperative IOP. MIGS can be expected to lower IOP only moderately and reduce the need for medications in cases with mild disease. For more severe disease a bleb-forming technique such as conventional surgery is likely to result in lower IOP and is therefore preferred. The discussion on the use of conventional surgery is beyond the scope of this Guide.
There was consensus regarding some aspect of the use of cataract surgery combined with innovative glaucoma surgery, namely:

- Whenever the clinical condition allows, sequential surgery with phacoemulsification performed initially should be considered.
- In cases where preoperative IOP is high or advanced disease is present, either bleb-forming devices as a standalone procedure or a combination of bleb-forming devices or techniques with phacoemulsification surgery should be preferred to MIGS.
- For combined procedures, it is recommended to perform phacoemulsification first, followed by inserting a device.

3.3 Clinical recommendations

Current evidence on MIGS and bleb-forming devices is not strong. Therefore, a significant effort has been made by the EGS to provide recommendations based on the consensus among groups of experts.
The consensus group considered ab-interno trabecular bypass surgeries appropriate for patients with non-progressing disease and an estimated target IOP in the “mid-to- high teens” range. Such procedures aim to reduce the burden of topical medications in individual patients; there was consensus on their good safety profile. The most appropriate surgical setting seems to combine these procedures with planned cataract extraction. In special circumstances, as in patients unsuitable for prolonged topical therapy, including those with ocular surface disease, poor compliance, and comorbidities this type of surgery may be used alone. Bleb-forming devices (Xen 45® and PreserFlo® at present) should be used by surgeons with good experience in traditional filtering surgery and wound healing modulation, familiar with bleb management, including the administration of intra- and postoperative

antimetabolites, the interpretation of bleb morphology and needling and/or revision procedures (strong recommendation).
Careful postoperative monitoring of the bleb is mandatory.
Although mid-term data show that bleb-forming devices are relatively effective, they are not currently recommended for patients requiring a very low target IOP. Traditional filtering surgeries are considered more appropriate in these phenotypes.

Choosing wisely

The consensus panel agreed on a number of actions that should be taken and others that should be avoided.

Things to do	Things to avoid
1. Check whether the angle is open and how widely	1. Do not place a device when the anterior chamber is shallow
2. Personalize your surgery according to the individual patient's needs and preferences	2. Do not perform MIGS if the target IOP is low
3. Use antifibrotic carefully	3. Do not perform angle surgery unless experienced in intraoperative gonioscopy
4. Audit your results regularly	4. Do not use bleb-forming devices surgeries if you don't have prior training and experience in bleb management
5. Consider cost-effectiveness	5. As a rule, do not perform more than one MIGS or bleb-forming device procedure targeting the same outflow pathway

3.4 Key questions

Convenience sampling based on geographical representation between EGS members was carried out for a survey focusing on identifying clinically relevant topics on innovative glaucoma surgeries. Initially, fifty European experienced surgeons participated. In this survey, each was asked to identify the 10 most relevant clinical questions regarding the indications and use of novel glaucoma surgeries. Thirty participants from 18 countries replied and all 248 pooled answers were collected and analysed. A total of 12 key questions were prioritised, of which some were further divided into sub-sections.

A literature review to provide the answers to those questions was conducted (see Chapter 2). Recommendations are proposed using GRADE methodology, according to the level of evidence: high, moderate, low, very low; as well as strength of recommendation: strong or weak. A strong recommendation should be interpreted as “we recommend” and/or “very relevant in clinical practice”, and a weak recommendation as “we suggest” and/or “less relevant in clinical practice”. Recommendations were elaborated among experts in three meetings between 2020 and 2022. Of note, several of the key clinical questions had a limited base of evidence. This relates to the lack of studies and data on several topics which can be described as relevant knowledge gaps in the field.
The recommendation for the 12 key clinical questions are listed below in Table 4.

Table 4 Key clinical questions
Conclusions were already addressed from the literature and required no consensus

	Question	Recommendation
1	For bleb-forming devices, which is the optimal antifibrotic treatment?	We recommend the use of Mitomycin C in all bleb forming procedures, with same criteria utilized for trabeculectomy surgery. Level of Evidence: Low Strength of recommendation: High
		Comments: Experience with antifibrotic use is important.
2	What is the optimal frequency, regimen and overall length of steroids/antibiotics use after surgery (MIGS and bleb-forming devices)?	We recommend the use of steroids and antibiotics post-operatively after bleb forming devices, with a regime similar to trabeculectomy. Level of Evidence: Low Strength of recommendation: High
		Comment: Regarding MIGS, there is currently no evidence to support any specific regimen, nor was there a clear consensus among the panel.
3a	What is the indication and optimal technique for needling or revision in bleb-forming devices: when, how and how many times?	Recommendation: Surgical revisions of bleb-forming interventions are preferred over needlings (particularly in Preserflo) because of their perceived longer lasting results. Level of Evidence: Low Strength of recommendation: Moderate
		Comment: No consensus reached on exact timing, exact technique and number of attempts.
3b	Should we use antifibrotics during needling or bleb revision (and if so which molecule and at which dose)?	We recommend the use of antifibrotics agents in combination with needling or bleb revision. Level of Evidence: Low Strength of recommendation: High
		Comment: No consensus between which type (5-FU vs MMC) and dose.
4	What is the relative safety of the different classes of MIGS and bleb-forming devices?	Conclusion: MIGS are safer than bleb-forming Devices. Level of Evidence: High
		Comment: Both MIGS and bleb-forming procedures carry risk of complications. However, MIGS seem to have a lower rate and severity of adverse events. Of note, one MIGS device has been taken of the market due to safety reasons. Safety as an outcome and how to measure complications is detailed in Chapter 7 and 8.4.3.2.

Table 4. Part 2

	Question	Recommendation
5	What are the long term outcomes of MIGS and bleb-forming devices compared with traditional glaucoma surgery? (i.e. with trabeculectomy and nonpenetrating surgery (NPGS))	Conclusion: Trabeculectomy remains the most effective glaucoma surgery in terms of IOP-lowering. Level of Evidence: High
		Comment: Consensus was that NPGS are likely more effective than MIGS devices. Bleb-forming devices have the potential to lower IOP levels similar to some types of NPGS.
6	What is the relative effectiveness of different MIGS (angle stents, cutting and dilating - same subgroups) and bleb-forming devices?	Conclusion: Bleb-forming devices are more effective in lowering IOP compared to the different MIGS devices. Level of Evidence: Low
		Comment: There are few high-quality comparative studies between MIGS. While some RCT suggest superiority of MIGS in combination with phaco over phaco alone the clinical value and long-term results remain to be proven. Studies directly comparing MIGS to bleb-forming procedures are not available. Indirect comparative data from the literature supports the conclusion.
7	Are there differences in outcomes other than IOP among different surgical techniques such as visual field or structural progression?	Level of Evidence: There is little evidence.
		Comment: Knowledge gap addressed in Chapter 8.
8	What is the recommended surgical intervention after initial MIGS or bleb-forming surgery failed?	We recommend not to do more than one MIGS or bleb-forming device procedure targeting the same outflow pathway. Level of Evidence: Low Strength of recommendation: High
		Comment: No consensus on what the second surgery should be after a failed bleb-forming device.
9	What is the cost benefit ratio for MIGS and subconjunctival devices versus trabeculectomy?	Conclusion: Insufficient evidence to guide the conclusion on cost-effectiveness versus conventional surgery. Level of Evidence: Low
		Comment: Knowledge gap addressed in Chapter 3.5.
10	Does previous MIGS/bleb-forming surgery have an impact on feasibility and outcomes of subsequent conventional glaucoma surgery?	Conclusion: A failed MIGS procedure is unlikely to have an impact on later conventional glaucoma surgery. However, bleb-forming procedures may impact conventional glaucoma surgery. Level of Evidence: Low Strength of recommendation: Moderate

Table 4. Part 3

	Question	Recommendation
11	Is there a loss of efficacy of different MIGS and subconjunctival devices when phacoemulsification is performed months/years afterwards?	Conclusion: Phacoemulsification may have a detrimental effect on bleb-forming device function when performed at a later stage. Recommendation: When the severity of the disease allows, sequential surgery with phacoemulsification performed initially should be considered. Level of Evidence: Low
		Comment: Due to lack of data, the conclusions were partially extrapolated from the repercussion of phacoemulsification on trabeculectomy, as stated in the EGS Guidelines.
12	Are there differences in QoL with subconjunctival devices and MIGS compared with trabeculectomy?	There is no evidence to inform this question.
		Comment: This was identified as a knowledge gap and a discussion on the effectiveness of current instruments for measuring QoL are addressed in Chapter 6.5 and 8.4.3.3.

This is a rapidly changing field; new devices and modifications of existing devices and techniques are emerging

Table 5 Non-Cochrane systematic reviews with acceptable quality evaluating novel glaucoma surgical procedures

PMID	Title	Year	Author
30728930	Comparing iStent versus CyPass with or without phacoemulsification in patients with glaucoma: a meta-analysis.	2019	Fard MA, Patel SP, Pourafkari L, Nader ND.
28850575	Minimally-invasive glaucoma surgeries (MIGS) for open angle glaucoma: A systematic review and meta-analysis.	2017	Lavia C, Dallorto L, Maule M, Ceccarelli M, Fea AM.
29258404	Xen 45® Gel Implant: a new surgical approach in glaucoma.	2018	Chaudhary A, Salina L, Guidotti J, Mermoud A, Mansouri K.
26426659	Comparison of Efficacy Between Endoscopic Cyclophotocoagulation and Alternative Surgeries in Refractory Glaucoma: A meta-analysis.	2015	Yang Y, Zhong J, Dun Z, Liu XA, Yu M.
28740733	When Is Evidence Enough Evidence? A Systematic Review and meta-analysis of the Trabectome as a Solo Procedure in Patients with Primary Open-Angle Glaucoma.	2017	Chow JTY, Hutnik CML, Solo K, Malvankar-Mehta MS.
NA	iStent® for open angle glaucoma: Standard or emerging care?	2017	Asselin G, Drolet R, Toren A, Coulombe M, Rhainds M.
NA	Glaucoma Schlemm's canal stent insertion: A systematic review.	2016	Jo S.

PMID	Title	Year	Author
26018579	iStent® as a Solo Procedure for Glaucoma Patients: A Systematic Review and meta-analysis.	2015	Malvankar-Mehta MS, Chen YN, Iordanous Y, Wang WW, Costella J, Hutnik CM.
26147908	iStent® with Phacoemulsification versus Phacoemulsification Alone for Patients with Glaucoma and Cataract: A meta-analysis.	2015	Malvankar-Mehta MS, Iordanous Y, Chen YN, Wang WW, Patel SS, Costella J, Hutnik CM.
27413541	iStent® Trabecular Microbypass Stent: An Update.	2016	Resende AF, Patel NS, Waisbourd M, Katz LJ.
30473602	Efficacy and Adverse Event Profile of the iStent® and iStent® Inject Trabecular Micro-bypass for Open-angle Glaucoma: A meta-analysis.	2018	Popovic M, Campos-Moller X, Saheb H, Ahmed IIK.
30663456	Cost-effectiveness analysis of standalone trabecular micro-bypass stents in patients with mild-to-moderate open-angle glaucoma in Canada.	2019	Patel V, Ahmed I, Podbielski D, Falvey H, Murray J, Goeree R.
26733487	Review and meta-analysis of ab-interno trabeculectomy outcomes.	2016	Kaplowitz K, Bussel II, Honkanen, R, Schuman JS, Loewen NA.
NA	Novel glaucoma procedures: A report by the American Academy of ophthalmology.	2011	Francis BA, Singh K, Lin SC, Hodapp E, Jampel, HD, Samples JR, Smith SD.

3.5 Cost-effectiveness of innovative surgery

Health economic evaluation is important for understanding the costs and value of all diagnostic and treatment interventions in order to guide clinical decision-making and resource allocation.[20] An intervention cannot be cost-effective if it is more costly and clinically less effective than other interventions.

One systematic review evaluated the clinical outcomes in randomised clinical trials (RCTs) comparing MIGS with trabeculectomy or other therapies, observational studies, and other non-RCTs published from 2005–2016.[21] For economic evidence, trials on cost-effectiveness, cost-utility, cost-benefit, cost-consequences, cost-minimization, the cost of illness, and specific procedure costs were included in the risk of bias assessment in all studies. Due to limited available evidence on the efficacy and effectiveness of MIGS, their cost-effectiveness was unclear, i.e., whether the cost of using MIGS would be outweighed by cost savings through decreased medication, a reduced need for further interventions, or decreased rates of disease progression. The authors concluded that larger randomised trials and real-world observational studies for MIGS devices are needed to better assess clinical and economic effectiveness.[21]

Similarly, the Health Technology Expert Review Panel in Canada (CADTH 2019) considered that there is insufficient evidence to make recommendations specific to the optimal clinical use and to the possible funding of MIGS by healthcare providers. Uncertainties were apparent, and the authors highlighted that there is the need for detailed reporting of results stratified by patient characteristics, valid and reliable measures of direct, patient-relevant outcomes, and long-term evaluation of clinical effectiveness, adverse events, harms, and cost-effectiveness. (www.cadth.ca/brief-optimal-use-minimally-invasive-glaucoma-surgery- health-technology-assessment)

Clinical trials evaluating health interventions, including glaucoma surgery trials, often featured suboptimal reporting of harm outcomes such as underreporting of withdrawals or losses to follow-up because of adverse effects irrespective of published guidelines on trials design.[22-24]

The lack of good evidence on the comparative effectiveness of different glaucoma treatments, not so much on IOP-lowering pressure but on preventing disease progression was noted.[25] This statement is true for different medicines, lasers, and surgical interventions and is reflected in the wide variety of glaucoma surgery techniques and postoperative follow-up regimens for each techniques and among surgeons using the same technique.[26] As part of the 2020 update of the EGS Guidelines, systematic reviews of interventions for glaucoma conditions published before August 2019 and all non-Cochrane systematic reviews of interventions for glaucoma conditions published between January 2014 and August 2019 were assessed for reliability.13 Among the 49 reviews considered reliable important limitations were noted on the value of information because of the uncertainty of the evidence and small, sometimes clinically irrelevant differences noted between interventions. High-certainty evidence was reported for a few topics like: reducing IOP helps prevent glaucoma and its progression, prostaglandin analogues are the most effective medical treatment for lowering IOP, laser trabeculoplasty is as effective as medical treatment as a first-line therapy in controlling IOP, conventional filtration surgery (trabeculectomy) is more effective than medications in reducing IOP. The evidence was found to be weak regarding the effectiveness of MIGS.[13]

Although MIGS seems to have gained popularity in the surgical management of glaucoma the evidence in long-term effectiveness remains lacking.[12,27] Additionally, reliable

cost-effectiveness and quality of life indicators have not been established by investigator-initiated randomized trials of sufficient size and duration.[28] In a small sample of patients, there was no significant difference between trabeculectomy and MIGS in the quality of life 6 months postoperatively. In the trabeculectomy group the intraocular pressure was significantly lower and the number of medications was significantly decreased than in the MIGS group.[29]

A cost-effectiveness simulation model within the US Medicare system showed that trabeculectomy appeared to be a preferred treatment strategy over the Preserflo® microshunt.[30] Obviously, when evaluating the published simulation models on cost-effectiveness, the overall low level of evidence of MIGS on clinical effectiveness with short follow-up times has to be carefully considered.

The evidence for MIGS being less costly and leading to better health outcomes compared to conventional surgery is missing

4. Recommendations for surgical innovation in glaucoma

Surgical innovations comprise new techniques, modified strategies, and innovative instruments.[31]

The conception of an innovation requires creative thinking without excessively stringent restrictions; developing it and assessing its value requires systematic order. Innovation and evaluation must progress in parallel. The IDEAL collaboration (idea, development, exploration, assessment, long-term follow-up to improve the quality of research in surgery) offers a structured approach to capture both innovative surgical thinking and evaluation for subsequent validation. The IDEAL collaboration began in 2009 with an objective of improving the safety, transparency, and effectiveness of surgical advance introduction and evaluation and being accepted in many surgical areas although it is not yet widely discussed in ophthalmology.

Traditional surgical procedures for glaucoma such as trabeculectomy and glaucoma drainage tubes have been used for decades. With the development of MIGS and other innovations, several unique devices and interventions were rapidly introduced, allowing a more individualized approach. However, despite their growing popularity, the bulk of these innovative surgical methods are still in their infancy due to inadequate evidence and absence of long-term follow-up to demonstrate their advantages over conventional approaches.

Given the complexity of the disease and the many subtle variations inherent to surgery, like the experience and training of the surgeon, the expertise of the team, the available infrastructure, patient characteristics and postoperative care, evaluating new surgical techniques in glaucoma presents numerous obstacles. Notably, appropriate outcome selection, masking outcome assessors, surgeon learning curves, and longer-term monitoring are concurrent challenges in designing RCTs to evaluate novel glaucoma surgeries.[32]

The IDEAL framework and recommendations describe the phases of surgical innovation and provide a road map for how surgical approaches should be evaluated at each level, offering coherence, structure and advice.[33,34]

4.1 IDEAL phases

A summarized description of the IDEAL phases is provided here in Table 6.

Table 6.

Phase 1
Results in a case report or a short case series describing the first use of a new technique in humans, often spurred by the need of a novel solution to a clinical situation. The Declaration of Helsinki highlights the significance of transparent reporting of research procedures and encourages prospective registration.44 Despite the apparent simplicity of applying these principles, the early stages of innovation may only become obvious in hindsight. A surgeon may first use a novel method to solve an otherwise difficult situation. Upon repetition, the surgeon may become conscious of having uncovered something possibly beneficial. Consequently, the first two steps of this model may be substantially finished before the novel character of the procedure is recognized. Transparency is required in patient selection, the informed consent procedure, and the description of the setting (including operator/team characteristics), location, and timing. In addition, a clear and comprehensive explanation of the technique/device, including patient safety monitoring procedures and appropriate pre- and post procedure care, must be included. Visual aids like pictures and videos are advantageous, and each patient's adverse consequences must be documented. The outcome measures used should be standardised and validated. Based on the findings of Phase 1, it will be possible to determine whether it is desirable to continue with further patients and to address potential risks and preventive measures.[45]

Phase 2a
Will lead to case series reporting the results after refinement of the technique. Reporting during this phase must include the following: selection criteria, eligible patients selected, a clear description of the procedure detailing the variation and clinically relevant outcomes and complications. Whenever feasible, all relevant result data should be integrated into a complete table or graph so that the link between method adjustments and outcomes may be readily shown. Learning curves are also a significant factor in this phase, and clear sequential outcome reporting of all cases should be conducted with no omissions. Phase 2a results will be used to evaluate whether the technique and outcomes have reached stability in the hands of the current team and to establish whether the technique is ready for evaluation in a prospective, multicentre IDEAL phase 2b study. The surgeon, the institution, and their ethical committee should reach a consensus on who is accountable for ensuring risk minimization.[45]

Phase 2b

Entails the exploration of the new technique using prospective and collaborative cohort studies. At this stage an assessment metric for how well the operator or team adheres to the methodology might be beneficial. Furthermore, documenting the operator's or team's learning curve using recognised objective quality indicators may be advantageous. Detailed descriptions of the primary and secondary outcome measures and statistical methodologies are needed. It is critical to consider how to develop and execute future RCT studies while considering surgeon preferences. Concerning the scheduling of randomised trials, theoretical justifications for early randomisation are weighed against practical considerations for delay. The learning curve will probably influence which surgeons engage in randomised trials and when they do so.

Phase 2b will provide the interpretation of data and evaluation of the suitability of proceeding to an RCT or a pilot/feasibility study. In this regard, consensus should have been obtained on the following:

- Standard technique (including accepted variants) and quality standards based on experience
- Target patient population and indications
- Outcome measure(s) (including estimated power calculation of the primary outcome)
- Comparator treatment for a trial
- Willingness among operators and patients to accept randomization.[45]

Phase 3

In the previous stages, the focus was on making a new technique and describing its results. In stage 3, the goal is to determine how well this new technique works compared with current standards. The most important thing is to determine the best comparator. At this stage, randomised controlled trials are the gold standard for comparing efficacy between conventional and innovative interventions.

Surgical randomised studies may be impractical for ethical or logistical reasons, such as recruiting challenges or lack of equipoise among surgeons. In these instances, other designs may be needed, such as parallel group non-randomised studies, expertise-based randomised trials, tracker trials, controlled interrupted-time series studies and step-wedge designs.[36,46-48]

Phase 4

Focuses on long-term evaluation, ideally through prospective databases and registries to assess innovations for rare side effects, long-term outcomes and for variations in outcome. Only key outcomes should be pursued to encourage complete data entry.

4.2 Training

Novel techniques require the acquisition of new skills. For experienced surgeons such training might include direct observation of a colleague during surgery or recorded video material, performing surgery under the supervision of an expert, enrolling in a formal training programme or practising in a simulation lab.

To establish competence the surgeon approaching a new technique needs a mentor with expertise in such a method to supervise a certain number of procedures. This training must be conducted in the appropriate setting and time to ensure the safety and efficacy of the new approach. Structured training programmes or manufacturer accreditation courses may ensure that surgeons are adequately trained in a novel surgical technique. As always during the learning curve period when a surgeon gains proficiency in a new surgical technique, patients may be exposed to a greater risk of complications.

4.3 Safety and consent

During the patient information and consent-obtaining process, the surgeon must adapt the discussion to each particular patient to ensure that they are informed on any significant risk and on possible alternatives. This is more challenging when a novel technology is involved, especially when only a limited amount of possible risks and rewards are known.

It is crucial that patients comprehend that a procedure is novel and must be informed throughout the consent process. The essential information to be included in the informed consent have been proposed.[36]

An investigation has been conducted to determine which information is considered important by both patients and doctors.[37] Eighty percent of patients answered that they would not consent to surgery if they did not know whether it would be the surgeon's first experience.37

If precise outcome data are available, such details are to be shared with patients. It is the surgeon's responsibility to ensure that the patient understands the information they are given well enough to objectively weigh the risks and benefits of a new procedure.[38]

4.4 Clinical governance

RCTs on surgical techniques that vary substantially from standard practice must be supported by stringent clinical governance procedures. It is recommended that an institutional surgical innovation committee be established to oversee the evaluation of surgical innovation.

This can be on a local, regional, or national level and the approach ought to be standardised and perhaps centralised to allow access to specialist expertise. When evaluating innovations, the goal is to strike a balance between the need for prudence and the opportunity to enhance patient outcomes by introducing surgical innovations. The committee should guide such a process. For purposes of accountability, research integrity, and clinical governance, all human trials should be recorded in publicly accessible worldwide databases. Protocol registration offers several advantages. It ensures that information about ongoing trials is accessible to the public and reduces the number of RCTs that repeat the same function twice. Registration facilitates adherence to globally accepted ethical standards, prevents the modification of primary endpoints based on findings during intermediate analyses, and ensures that the trial is conducted and analysed as initially intended. This allows researchers to enhance the quality of study designs and the dependability of scientific findings.[34,39]

4.5 Conflicts of interest

Surgeons must disclose any potential financial or professional conflicts of interest, and provider organizations must be aware of any conflicts that may arise for both the surgeon and the organization, such as the surgeon's affiliation with a manufacturer of a novel technology.[40] Conflicts may also emerge when a patient is referred to or specifically requests to be treated by a specific doctor because he/she is known to be performing innovative surgery. This could put pressure on the surgeon and the possibly influence the choice of procedure. There also may be financial incentives towards a specific technique or device. The natural desire to achieve good results when deploying a supposedly better, new technique may lead to bias in patient care and on data handling and interpretation.[41]

4.6 Summary

The IDEAL collaboration began in 2009 with the objective of making safer, more transparent and more effective the introduction and evaluation of surgical advances (Table 6). IDEAL is becoming accepted in all areas of surgery; however, it is not yet widely discussed in ophthalmic research. We note that no patients with eye diseases or ophthalmic surgeons were engaged in the recent development of a core outcome set (COS) to assess novel surgical techniques and equipment.[42] A recent systematic review analysis of RCTs that examined the efficacy and safety of novel surgical techniques in ophthalmology, including glaucoma, revealed that crucial aspects of study design and execution were often absent.[43] These components include the impact of surgeon's expertise, the learning curve on the new approach, quality assurance, reproducibility of the intervention, disclosure of conflicts of interest and trial registration. This finding supports that surgeons, investigators, research organizations and journal editors should do more to guarantee that clinical trials evaluating novel surgical techniques in ophthalmology adhere to the fundamental standards suggested by the IDEAL partnership. The IDEAL guidelines help innovators, methodologists, and device manufacturers on how to use the IDEAL framework by identifying the most crucial outcomes to be assessed at each step of the innovation process.

5. Overview of study designs

The journey of surgical innovation starts with an original idea, followed by development and careful evaluation, all underpinned by proper governance.

The IDEAL framework offers a structured surgical innovation approach that includes four phases or stages.[45,49] Glaucoma surgeons should adopt a similar process (see Table 6).

Typically, phase 1 involves a novel solution and generates a case report or a short case series. A detailed explanation of the technique should be offered. If the clinical outcomes and safety profile of Phase 1 appear positive, the next phase can be planned.[45]

Phase 2a, most often a case series, will determine if the technique has reached stability and is ready for evaluation in a prospective study. Phase 2b, usually a pilot cohort study, provides feasibility data to address a subsequent RCT.

The goal of phase 3 is to compare the efficacy between conventional and novel interventions with high-quality RCTs. Phase 4 focuses on long-term evaluation to assess innovation for uncommon safety events, variations in outcomes and long-term evaluations. This should ideally be performed using prospective databases, registries and/or electronic patient records (EPR) with high user coverage. We discuss Phases 3 and 4 in more detail below.

5.1 Randomized controlled trials in glaucoma

Since the first such study appeared in the 1940s, RCTs have generally been accepted as one of the greatest advances in medicine of the 20th century. RCTs underpin many changes in medical practice and provide evidence on which to base current therapies. An RCT is a study design that minimizes bias and confounding, both frequently affecting medical evidence. Consequently, data from an RCT or a series of RCTs are considered the highest-quality evidence. Any new technology claiming superior efficacy to another already in use should be tested with an RCT.50 RCTs are costly to perform in terms of direct cost. There is also an opportunity cost, for example, indirectly limiting the funding of other health care areas or research strategies. RCTs take time and often several years are needed before outcome data are available; meanwhile clinical practice may change also following new research findings. RCTs have limitations regarding external generalizability, as study populations may not represent the population of a clinical practice. Typically, RCT participants are younger and healthier than the general population; disadvantaged and ethnic minority groups tend to be underrepresented.[51]

There are many uncertainties regarding optimum strategies to design and conduct trials. Trial Forge (www.trialforge.org/about/) is an initiative focused on improving trial planning and implementation.

A difficulty in designing glaucoma trials is the slow progression of the disease in the majority of treated patients. Shorter-duration trials for glaucoma have been advocated but are realistic mostly in studies with anticipated large outcome differences between arms. This consideration would apply to trials comparing an effective treatment against placebo: the 'UK Glaucoma Treatment Study' UKGTS trial is a notable example[52,53].

In contrast, glaucoma RCTs comparing two effective treatments have to contend with a likely small difference in relative treatment effect, requiring increased statistical power via a substantially larger number of participants or a longer follow-up period.

Loss to follow-up is a significant challenge of longer follow-up periods, particularly in an older patient cohort. In a 10-year trial, it would not be surprising to see a 50% loss to follow-up rate with a 25% rate of death due to the old age of the population increasing the risk of bias due to attrition.

Balancing the assessment of short-term surgical morbidity and long-term success is also challenging, as is finding an ideal primary outcome measure.

Quality of life (QoL) measurements in glaucoma trials have been advocated but may not be adequate, not least because the impact of glaucoma on vision-related QOL measures is only detectable in very advanced disease,[54,55] while most glaucoma trials on both medications and surgery devices are conducted on patients with early glaucoma. Limitations of QoL as an outcome measure for glaucoma trials have recently been highlighted.[56]

5.1.1 Randomised controlled trials evaluating surgical innovations

Surgical RCTs are particularly challenging to perform and unsurprisingly are fewer in number. Designing a surgical RCT is particularly difficult because surgery is a complex intervention with multiple factors influencing the outcomes, such as surgeon skills, learning curve, team performance and the effect of pre and postoperative care. Further details on how to address methodological challenges in surgical trials can be found elsewhere.[36,37,42,43,45,57] Regarding RCTs to assess surgical innovations for glaucoma, it would be efficient and valid to use IOP as the primary outcome at 1-2 years without the need for long-term follow-up and formal evaluation of disease progression within the trial. Longer-term effectiveness and safety data could be captured via electronic patient records or EPR (see Chapter 5.1.2). Ethical considerations in surgical trials pose significant issues. Open communication on risks and benefits and the uncertainty of the outcomes must be addressed when discussing possible trial participation with patients.[58]

When a new procedure is being introduced in clinical units where good outcomes with existing procedures are common, surgeons may be less prepared to recruit and vice versa. Whilst the results would be valid, there would be issues of generalisability as potentially the

control outcomes in an RCT examining a new treatment may be less good than established gold standards for the existing procedures. On the other hand, some units may be 'beacon' centres with particularly good outcomes that are not seen elsewhere; this will impact the generalisability of the trial outcomes.[59]

An important barrier in surgical trial recruitment is that both clinicians and patients can find the randomisation element difficult to accept, especially when one arm involves an intervention that is perceived to be more invasive, e.g., surgery versus medication; thus eligible patients may decide not to take part. 'Patient preference trials' have been proposed to address this issue (e.g., the REFLUX trial[60]). If there is a lack of equipoise among surgeons or a difference in skills, an 'expertise-based trial' design can be considered (e.g. the KAT trial[61]). Adverse effects in surgery may be uncommon but can be significant. In most cases, clinical trials do not have the statistical power to detect differences in rare adverse effects.[23] Uncommon side effects, especially if severe, are extremely important in comparing surgical techniques; side effect risk quantification is impossible in RCTs. The problem of accurately quantifying severe, sight-threatening adverse effects, such as endophthalmitis after intravitreal injection, with an incidence of, for example, <1:1000 cases, is common across ophthalmology subspecialties. Large real-world data and registries are important, but the optimal approach is most likely the wider adoption of EPR systems, which effectively undertake a 'running audit' of all interventions and accurately quantify the incidence, severity, and temporal patterns of rare severe complications (see Chapter 5.1.2). The wider use of EPRs is also the optimal method for surgical 'quality control', i.e., the real-time monitoring of the surgical complication rates of different surgeons performing the same, perhaps novel, technique.

5.1.2 'Real world data' and the value of EPRs

There is a long tradition of retrospective studies reporting surgical outcomes by a single surgeon or groups of surgeons, as well as comparisons between experienced and less experienced surgeons or the impact of different approaches to surgical training.[62,63]

A more recent development has been the use of data held in EPR systems to undertake larger audits with much larger numbers, which have higher precision to detect less common outcomes (see below).

There are, however, important disadvantages in the use of retrospective audits of surgical outcomes, including large EPR-derived datasets.

The most obvious drawback is the perennial risk of missing data. This can happen accidently or deliberately. The former is in case of lost data points often due to incomplete data collected on some visits. The latter in the form of 'cherry-picking' cases with more favourable outcomes. This problem can be mitigated by mandating the use of consecutive surgical cases in a series. This approach was used in a UK-based multicentre retrospective audit of trabeculectomy surgery, which required a selected group of UK glaucoma surgeons all of whom used a similar surgical techniques to provide data on 50 consecutive trabeculectomy cases over a specified time window.[64]

Further problems with retrospective audits include the lack of a prospective trial hypothesis with predetermined outcome measures. The risk here is that the researcher being aware of results could establish a study hypothesis in retrospect, perhaps towards a desirable study outcome. This is a peculiar risk in surgical research if the researcher is an enthusiast (or 'beacon') for the surgical technique being studied. In an RCT this occurrence is discouraged by openly registering and publishing the protocol and statistical analysis plan before any of the data are seen or collected and by avoiding secondary analyses after the data are collected.
The advantages of real-world data include better generalisability. The use of very large datasets obtained from EPRs facilitates an estimation of the incidence and impact of uncommon or rare severe complications. This is an important issue in establishing the safety of medical or surgical treatment and in the past it has benne accomplished by post-marketing surveillance, the "yellow card" reporting system of the UK. Establishing safety is, important in surgical innovation, as highlighted by recent well-publicised scandals in which rather rare but devastating complications of new surgical devices were overlooked for want of proper premarketing safety data, and high-quality postmarking surveillance was lacking, e.g., an absence of a well-managed registry monitoring the adoption of a novel device.[65] The regression to the mean affects many studies in glaucoma. It is therfore a particular issue in studies where recruitment depends on whether a patient is 'stable'. Where the recruitment criterion (IOP) is closely related to the outcome e.g., IOP change or less commonly visual field (VF) change, then the regression to the mean is inevitable. When a potential patient has an IOP higher than previously measured (or higher than a 'target' IOP), they are more likely to be recruited but also relatively likely to have a lower mean IOP on a subsequent examination because point IOP measurements vary. The regression to the mean effect is larger than commonly realized, often in the 5-6 mmHg range.[66] This is a particular issue in non-comparative evaluations of interventions with a relatively small effect on IOP, such as MIGS. While not a cause of bias in a comparative RCT (as the regression to the mean will affect equally to both interventions) it is possible that the efficacy will be overestimated.[67] The history of EPRs in ophthalmology is relatively short. Naturally, the widespread collection of everyday clinical data from glaucoma patients in a digital format, including IOP, imaging, and visual function tests, developed gradually with the availability of hardware and software allowing these approaches to be undertaken in most clinical environments. Equally importantly, the digital storage infrastructure and means to access the data at the bedside/in the clinic has made realistic EPRs which can fully replace all paper notes only in the last 20 years.
A UK-developed EPR, called, Medisoft, which the late Robert Johnston developed, has been used in over half of UK eye units for over 18 years. With anonymised data-sharing between centres and the wealth of data now available from many years of Medisoft use, the Royal College of Ophthalmologists 'National Ophthalmology Database' has allowed publication of ground-breaking 'real-life' prospective audits of commonly performed eye operations, e.g., cataract surgery. The first publication arising from a Medisoft-aided prospective audit of 180,114 cataract surgeries across the UK, which included surgery performed by consultants and a range of nonconsultant surgeons (including trainees), was able to quantify rare complications rather precisely, e.g., endophthalmitis, and showed, for example, that if posterior capsular rupture (PCR) occurred, the risk of endophthalmitis was increased eightfold. Likewise, PCR was associated with a 42-fold higher risk of postoperative retinal detachment.

Other interesting findings included an overall 1.95% PCR rate across all surgeons, with a somewhat higher rate for trainees.[68]

Similarly, there have been some notable 'real-life' glaucoma studies where large, prospectively collected EPR datasets have been utilized, including the use of selective laser trabeculoplasty (SLT) in a large UK-based analysis that used Medisoft.69 These studies, while exploiting the undoubted value of very large datasets available from long-established EPRs can offer widely clinically applicable insights that may not always be readily obtainable from RCTs undertaken to answer a related clinical question.

The particular strength of EPRs is the potential for obtaining very large datasets, as demonstrated by the UK cataract audit, allowing the precise quantification of rare complications: with a surgical technique as refined, safe and predictable as modern cataract surgery, the prevalence of serious sight-threatening complications becomes the most important rare side effect to measure precisely. It would be impractical to design an RCT powered to answer these important questions. The choice between an RCT and a prospective EPR-based audit is less important than the consideration of synthesising findings from all possible sources of data while being mindful of the pros and cons of each approach.

Important lessons have been learned from early experiences of using large EPR datasets to answer clinical questions, especially about the risks and benefits of surgical treatments; this information can be applied to aid the evaluation of glaucoma surgical devices.

5.1.2.1 Surgical registries

The disadvantages of both RCTs and retrospectively collected audit data in the evaluation of (especially) novel surgical devices in glaucoma, notwithstanding the potential of the growing importance of EPR, have focused interest on the use of formal registries logging the adoption of novel surgical devices.

Surgical registries have an advantage over audits in that the data are collected prospectively. With the wide adoption and use of a registry for a particular device, as the numbers of procedures logged grows with wider adoption, then the size of the dataset starts to become useful for detecting rare but potentially serious adverse effects of the novel device. There are obviously important qualifications considering how the registry is managed rather than an intrinsic shortcoming.[70] Sending outcome data to the registry should be mandatory for any surgeon conducting a novel procedure.

5. Overview of study designs

Several steps for successful surgical registries has been proposed.[70]

- steering committee to lead and oversee the registry;
- clear registry objectives;
- planning for initial and long-term funding;
- strategic national or international collaborations among key stakeholders;
- dedicated registry management team;
- consensus meetings to agree on the registry dataset;
- established data processing systems;
- anticipating challenges;
- implementing strategies to increase data completion.

• The Idea/Innovation, Development, Exploration, Assessment, Long-term follow-up (IDEAL) Framework has been developed to offer a structured approach to surgical innovation
• All steps involved in the development of new surgical techniques should be registered publicly
• Prospective case series studies are important for pre-trial evaluation
• Randomised trials should be used whenever possible to investigate efficacy
• Surgery is a complex intervention and trials evaluating novel surgical techniques are particularly complex to design and deliver
• Alternative prospective designs should be used when randomised trials are not feasible
• The widespread use of prospective databases and registries to monitor the efficacy and safety of novel surgical interventions is encouraged

6. How to present data from glaucoma surgical trials

Good Clinical Practice (GCP)

Successful glaucoma surgery stops or significantly reduces disease progression while not significantly affecting a patient's vision and quality of life. Theoretically, the best outcome measures to use when considering surgery outcomes would be closely related to visual function and quality of life. However, measuring these outcomes requires a large sample and a long follow-up period. Accordingly, surrogate endpoints have been used. There is compelling evidence that IOP reduction reduces the rate of glaucoma progression and that the degree of IOP lowering is associated with efficacy in reducing the deterioration of function. Therefore, IOP remains the principal endpoint in glaucoma surgery trials.

Reporting outcomes in glaucoma surgical studies has generally been inconsistent, complicating comparisons between unrelated studies and hindering the ability to reach a consensus in data interpretation. According to one report among 100 studies, 92 different IOP-related definitions of "success" were used.[71] The European Glaucoma Society and others have long ago proposed a simple system of reporting IOP outcome criteria.[3,72] This system was also recommended in the WGA Guidelines in 2008.[1]

The aim of this chapter is to provide a structured overview of endpoints when reporting glaucoma surgery data.

6.1 Intraocular pressure

6.1.1 Tonometry

Goldmann applanation tonometry (GAT) is the reference standard for surgical trials, and reporting GAT values facilitates comparison across studies. Regular calibration of the instrument is needed, particularly in a clinical trial setting. Ideally, each IOP measurement should include 2-3 readings at each time point, returning the tonometer dial to a random lower value prior to making the reading. Alternative frequently used instruments are air puff tonometers (i.e., Ocular Response Analyser® or other types) and the rebound tonometer (iCare® tonometer). Efforts to reduce the risk of investigator bias are important, e.g., a two-investigator technique. Central corneal thickness (CCT) may impact the IOP reading, over- or underestimating GAT reading. However, it should not influence the outcome in a clinical trial setting where two different interventions are compared and IOP is measured at baseline and each study visit.

6.1.2 Defining baseline IOP

The baseline IOP is essential for determining the degree of longitudinal IOP change per individual. Clinical parameters for preoperative IOP measurements are rarely standardised, as patients are typically recruited from a heterogeneous clinical population. The more commonly reported baseline IOP is the value at recruitment or prior to surgery. The baseline IOP can be determined either under therapy, after washout or in untreated cases. In patients with established disease, washed-out IOP measurements may not be desirable for safety reasons. Baseline IOP readings are mostly taken from patients treated topically with or without systemic drugs. Commonly the most recent IOP is used. Some studies have used the median of the last two or three measurements prior to surgery, which is a more robust approach but is not always feasible. Peak IOP as a baseline is considered too variable and may significantly skew pre/post comparisons. When the trigger for recruitment (high IOP) is closely related to the outcome (e.g., IOP change), then regression to the mean is inevitable, leading to a marked overestimation of the effect of surgery on IOP (see Chapter 5.1.2). This effect is likely to be less for studies where the decision for surgery is based on visual fields.

6.1.3 Target IOP

The main goal when undertaking surgery is to significantly reduce IOP, which should lead to a postoperative target IOP that is lower than preoperative values.
The EGS Guidelines promote individualized target IOP for routine clinical management. However, a predefined target IOP is a more appropriate outcome measure for a clinical trial outcome 'success' measure. Both an upper limit of IOP and a percentage reduction of IOP can be used. For example, in a study of patients with mild/early disease, a cut-off IOP of ≤21 mmHg with a percentage reduction of 25% might be considered reasonable, whereas for those with more advanced disease, corresponding figures of 18 mmHg and 30% or 15 mmHg and 40% might be appropriate. Using more than one set of criteria in the presentation of data is recommended.

6.1.4 Success as an outcome parameter

When an endpoint is achieved without additional medication after surgery, the result is generally referred to as "complete success" while "qualified success" is used if it is achieved with additional medication. The challenge in defining "qualified success" in comparative or randomized prospective studies is that reintroducing medication after surgery is not a standardized process but is decided at the surgeon's discretion and is vulnerable to bias. Similarly, the use of 'reduction in postoperative medication' as a primary outcome measure is likely to be vulnerable to bias. Postoperative reduction or discontinuation of medication

has been used as a primary outcome measure in various reports on MIGS RCTs.[12] Sometimes this is referred to as the proportion of patients who are 'drop-free'. While this gives an estimate of relative efficacy between procedures, the use of medication reduction as a parameter for success is questionable: Unless a previously defined treatment algorithm is used, postoperative medication is subject to the doctor's and patient's preferences and is susceptible to bias.

6.1.5 Failed IOP control, visual loss, and further surgery

Failure is defined as an IOP level above the pre-set target IOP usually measured at two consecutive visits or severe vision loss after surgery due to complications or the need for further surgical intervention. Minor interventions such as suturelysis, Nd:YAG laser goniopuncture, antimetabolite injections and needlings are not considered failure events but should nevertheless be reported. Complication reporting is covered in Chapter 7.

6.2 Visual acuity

Glaucoma surgery, while lowering IOP, should not have negative effects on visual acuity. Therefore, visual acuity should be considered a safety outcome. Reduction in best-corrected visual acuity (BCVA) of >2 Snellen lines, equivalent to doubling of logMAR values is generally considered a clinically relevant change and the reasons should be reported.
Of note, BCVA reduction is not suited to serve as a primary endpoint in surgical trials, as other factors unrelated to glaucoma surgery such as macular or retinal disease are common in these typically older study populations. BCVA should be tested with standardized methods pre- and postoperatively (e.g., ETDRS charts). Preoperative and final visual acuity at the study end can be summarized in a table or graphically depicted in a scatterplot. In case of very low vision, categories can be defined as hand movements (HM), light perception (LP) or no light perception (NLP). For statistical analysis, HM will be considered 1/800 (logMAR 2.3), LP 1/1600 (logMAR 2.8), and NLP 1/3200 (logMAR >3). A loss of ≥ 3 lines on an ETDRS, corresponding to a doubling of the visual angle (e.g., from 10/10 to 5/10), is considered a moderate visual loss. A loss of ≥ 6 lines, corresponding to a quadrupling of the visual angle (e.g., from 8/10 to 2/10), is considered severe. The percentage and causes of moderate and severe visual losses should be reported to evaluate the safety profile and compare surgical procedures.

6.3 Visual field parameters

Despite the subjective nature of VF testing and the confounding influence of media opacities such as cataracts, VF is the measurable parameter closest to functional impairment in glaucoma and is of general importance.
For practical purposes, at least 2 VF tests are required preoperatively for baseline, and a clear regimen of postoperative VF testing should be included in the study design.
The general weakness of many studies is the lack of a stringent postoperative VF regimen. The pre-and postoperative MD may be sufficient for shorter trials, such as in the early stage of innovative surgeries. A 2-year time horizon is relevant for more mature evaluation stages, and VF outcomes should be reported; to detect visual progression in such a relatively short period requires frequent testing.[53]

6.4 Structural outcomes

Structural outcomes are not usually used for early-stage evaluations in surgical innovation trials. In short-term studies, the sensitivity to detect change is poor, and issues such as floor effect in RNFL measurements in advanced cases, concomitant macular disease, and potential bias of cataract surgery arise. Imaging may play a role in long-term studies (>5 years).

6.5 Quality of life

Quality of life (QoL) measurements in glaucoma trials have been advocated but may not be adequate, not least because the impact of glaucoma on vision-related QOL measures is only detectable in very advanced disease,[54] and very many glaucoma trials of both medication and surgical devices are conducted on early glaucoma patients. Limitations of QoL as an outcome measure for glaucoma trials have recently been highlighted.[56]

6.6 Overall data presentation

Tables are recommended for reporting baseline clinical data and outcomes (including IOP, medication, visual function and complication).
Graphs are recommended to report on the following data:

- IOP distribution over the follow-up period
- Survival curves of surgical success (possibly showing more than one criterion)
- Scatterplot of IOP pre- and post-surgery
- Diagram or table of medication. It can be depicted as a bar diagram or as a table
- BCVA using scatterplots or tables

Some recommended graphical formats for the presentation of these data are presented in the following section.

6.6.1 Mean or median IOP values

Reporting averaged IOP values with a measure of data dispersion at a certain time point after surgery is common. Mean values ± standard deviations (M±SD) are often used. Standard error (SEM) should not be used. As IOP values rarely show a normal distribution, it is usually better to report data as median with interquartile ranges to describe the spread of data (Figure 4).

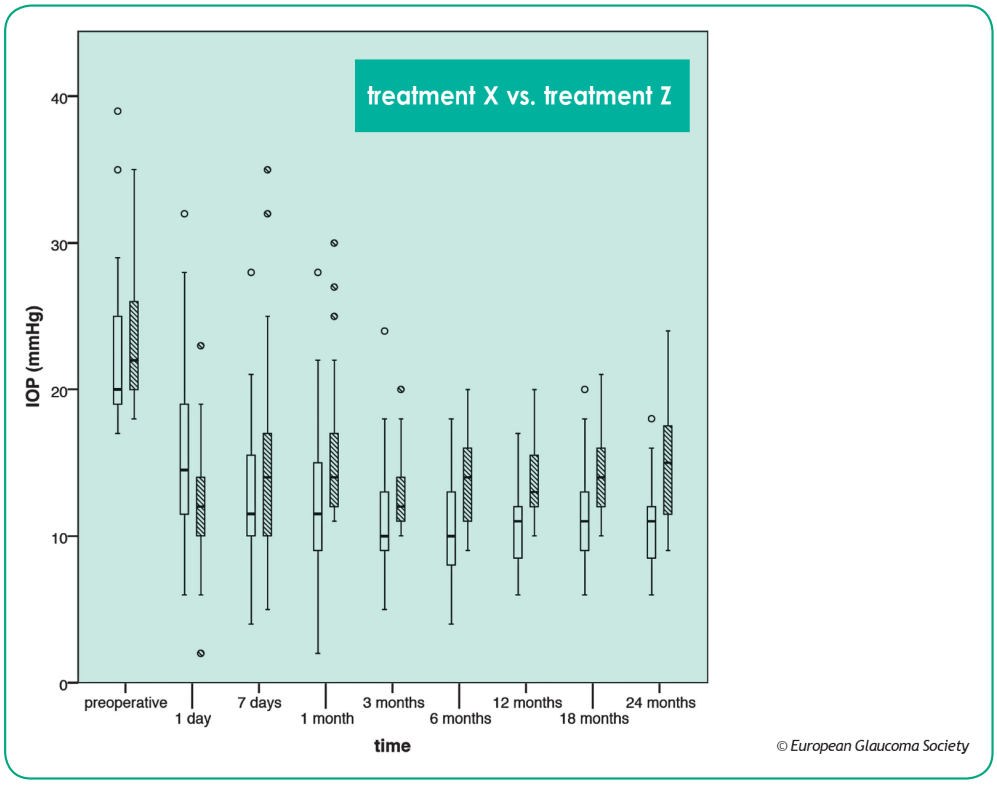


Figure 4. *Median IOP values (horizontal black line) and percentiles (boxes-quartiles = 25/75; whiskers = 5/95) given preoperatively and for a follow-up of 2 years. Single outliers are shown by circles. (Modified from: Matlach et al 2015).*[73]

6.6.2 Kaplan-Meier curve

Survival curves or Kaplan-Meier analysis of time to failure should be considered mandatory in the graphical representation of results. Survival is usually described according with a pre-defined target IOP success criteria. The survival curve should also document the numbers in each study group at all follow-up points, including censored points (Figure 5). If possible, the 95%-confidence interval should also be depicted.

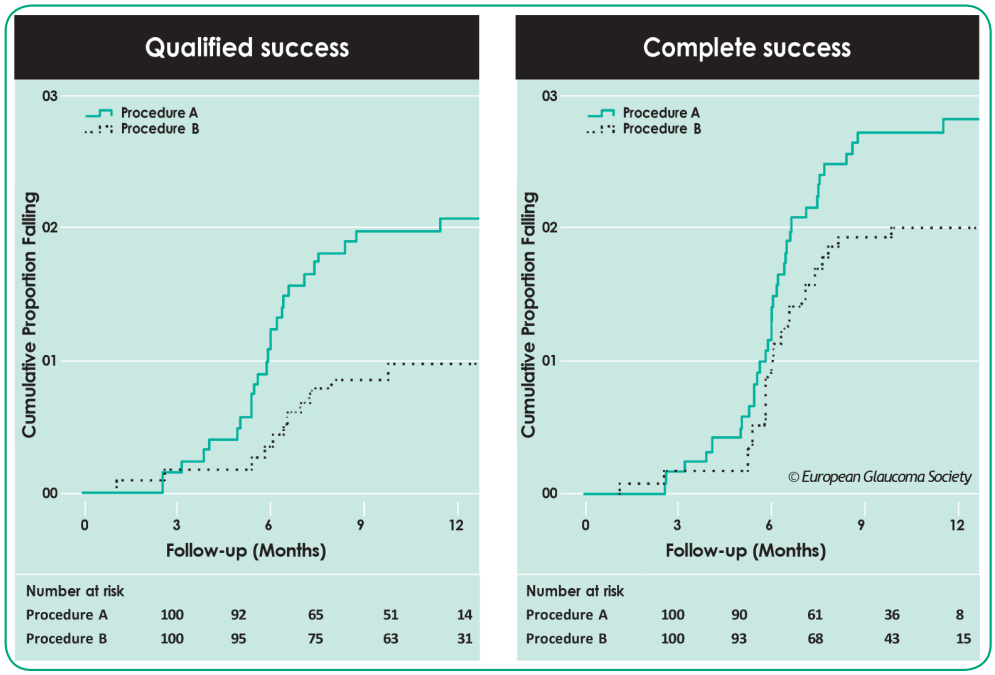


Figure 5 *Kaplan-Meier survival curves showing 1-year success rates (1-failure) given on the abscissa for two different 'success' criteria.*

6.6.3 Scatterplot

Scatterplots are particularly helpful. Each eye is represented by one point with baseline and postoperative IOP at a given time point plotted against each other. The diagonal line (y=x) represents no change in IOP. Therefore, eyes with IOP reduction are below the diagonal line. By using different symbols, eyes with '**qualified success**' or '**complete success**' can be separately visualized. Additional diagonal lines whose slope represents predefined thresholds of relative IOP reduction (i.e. 20, 30 and 40% changes) and horizontal lines representing thresholds of absolute IOP values (i.e. 12, 15, 18 and 21 mmHg) can be informative (Figure 6). The proposed scatterplot graph could be used if an author or reader wishes to superimpose their own success/outcome criteria.

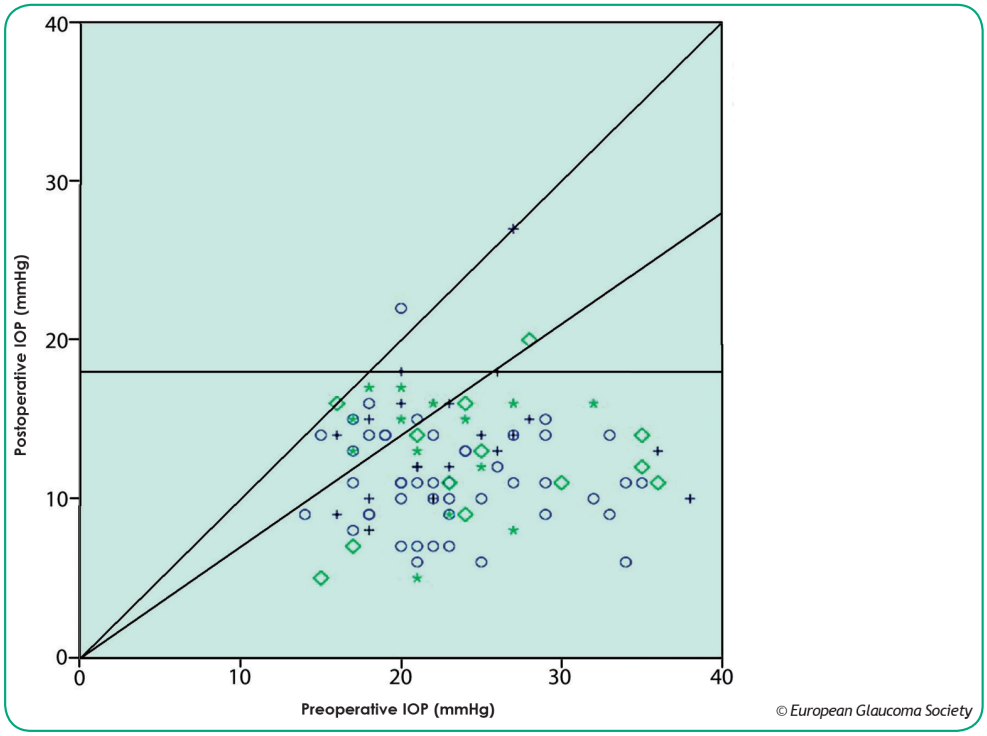


Figure 6 *Combined success criteria of ≤18 mmHg (horizontal line) and ≥30% lowering of IOP (lower oblique line) in a matched comparison of two surgical procedures. All but 3 eyes had an IOP of ≤ 18 mmHg. However, an additional 15 eyes did not meet the 30% criterion. Different groups can be depicted with different symbols: circles= eyes with procedure A without medication; crosses= eyes with procedure A with medication; diamonds= eyes with procedure B without medication; starlets= eyes with procedure B with medication. (Modified from: Glatzel et al 2021).*[75]

6.6.4 Preoperative versus postoperative medication

Postoperative IOP-lowering medication can be presented in a table that can be used in conjunction with a graph (e.g., an IOP scatterplot).

Reduction in IOP-lowering medications has been used as an outcome measure in numerous studies assessing MIGS devices; this is sometimes referred to as the proportion of patients who are 'drop-free'. While this outcome is relevant to patient care, it may lead to overinterpretation of the findings, as it often magnifies differences between study groups. Moreover, there is considerable potential for bias, particularly if treatment decisions are left at the discretion of treating clinicians. It is difficult to assess IOP-lowering medications without a standardized set of criteria for administering treatment, ideally controlled by an external masked trial centre.

Usually, a comparison between the average of preoperative versus postoperative/final medication is reported. If the number of medications in a cohort of patients is statistically analysed, median values (box plots) should be preferred because calculating mean values ± standard deviation often results in standard deviations below 0 due to the nonparametric distribution of low values.

6.6.5 Graphical representation of visual acuity

Preoperative and final visual acuity at the study end can be summarized in a table or graphically depicted. Averaging should use logMAR values because averaging decimal values is incorrect due to the logarithmic nature of visual sensory scales. For statistical analysis, HM will be considered 1/800 (logMAR 2.3), LP 1/1600 (logMAR 2.8), and NLP 1/3200 (logMAR >3) (see Chapter 6.2). Figure 7 presents an example of pre- and postoperative logMAR VA values in a scatterplot.

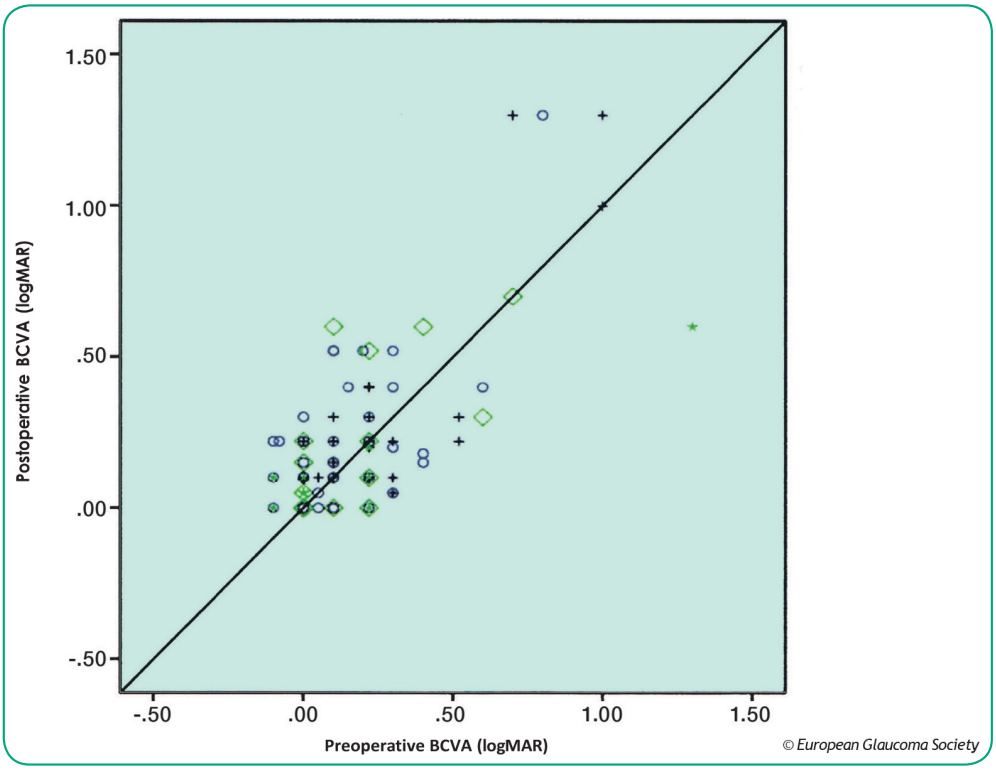


Figure 7 *Preoperative versus postoperative (at 2 yrs) logMAR visual acuity for two di erent matched surgical methods. Circles and diamonds show the BCVA values of the two surgical techniques of phakic eyes; crosses and asterisks show the respective pseudophakic eyes. (Modified from: Glatzel et al 2021).*[75]

6.7 Methods of analysis and reporting

The involvement of a clinical trials unit (CTU) and close collaboration with statisticians and researchers with expertise in designing and conducting trials and analysing data is essential. Some suggestions are offered below regarding how to describe and report data.

6.7.1 Descriptive statistics

Continuous variables should be statistically tested to determine if data are adequately modelled by a normal distribution and then should be described as the mean or median with dispersion measures (e.g., SD or interquartile range) accordingly. Categorical and nominal variables can be described with frequencies.

6.7.2 Minimal clinically important difference (MCID)

Published studies often evaluate surgical interventions by describing the difference in outcomes between two groups of patients to assess and compare their effectiveness.
In incisional glaucoma surgery, for example, absolute between-group or before-after differences in IOP are often reported as primary outcomes, and they are usually defined as significant only in statistical terms based on conventional hypothesis testing.
Nevertheless, in addition to the potential for type II error of inferential statistics which requires appropriate sample size calculations, a statistically significant difference might not necessarily correspond to an important difference from the clinical point of view.
Researchers are encouraged to define the minimal clinically important difference (MCID) for important outcomes in advance. The MCID can be defined as "the smallest difference in any outcome of interest that patients can perceive as beneficial or harmful". Consequently, the MCID is intended to represent the smallest difference to define two interventions as similar or different or to justify a change in the management of the disease. By applying this concept, authors can then calculate the sample size required to statistically detect the predefined MCID with appropriate confidence, avoiding wasting resources related to under- or oversampling.
Nevertheless, defining MCID is challenging when designing studies to assess and compare surgical innovations for glaucoma. It is even more challenging considering that MCID is a variable concept, and there can be multiple estimates for the same outcome across several factors, including the setting, health status, stage of the disease, and presence of comorbidities.
Most of the current glaucoma literature focuses on MCID for patient-reported outcomes, and no definition of MCID for IOP or other glaucoma-related clinical outcomes has been agreed. There are several proposed methods to determine the MCID for any given intervention, such

as distribution-based, expert opinion-based and anchor-based methods, the description of which is beyond the scope of this Guide.[76-78]
In the context of IOP, a survey conducted among glaucoma specialists in the UK and an expert discussion group of the European Glaucoma Society identified 2-3 mmHg as the MCID for surgical interventions for glaucoma.
Furthermore, attempts have been made to define the MCID for other outcomes pertaining to the efficacy domain, such as the proportion of patients who are "drop-free" after the surgical intervention. Provided that the implementation of standardized protocols for the reintroduction of hypotensive drops during follow-up is essential for the reliability of this outcome, the majority of EGS experts have determined that the MCID for this outcome should be between 20 and 30%.
Concerning changes in global indexes of visual fields, the majority of EGS experts judged that an MCID should be not less than 2 dB between interventions. Again, the MCID should be contextualized considering factors such as the length of follow-up, the characteristics of the population being studied and the nature of the surgical intervention under investigation.
Considering that no standards are yet defined or consolidated, especially when primary outcomes pertain to domains other than the efficacy domain, investigators are strongly encouraged to define the MCID and to describe the rationale and the methods they relied upon for its choice.

MCID

MCID is defined as "the smallest difference in any outcome of interest that patients can perceive as beneficial or harmful"
Authors should report the MCID used in their trial
The EGS consensus expert panel resulted in the following:

- IOP 2-3 mmHg
- Medication free: 20-30% of study subjects

6.7.3 Kaplan-Meier curves

Kaplan–Meier curves are highly recommended for IOP to describe and compare the between-group time-to-event in the clinical course after the surgical intervention using <21, <18, <15 and <12 mmHg thresholds. See also 6.6.2.

6.7.4 Missing data

It is highly recommended to use both the per-protocol and the intention to treat approach to analyses data. Additionally, the number of patients analysed at each time point of the follow-up must be reported for all outcomes.

6.7.5 Standards for reporting

The Consolidated Standards of Reporting Trials (CONSORT)[79] should be implemented for all randomized clinical trials.
Standards for reporting nonrandomized and observational studies are available in the literature and should also be implemented for early phase evaluations, e.g., IDEAL phase 1 and 2 stages[80] (extensions to the CONSORT and STROBE)[81].
In addition, the PROCESS (Consensus on preferred reporting of case series in surgery)[82] guideline may be considered to provide a structure for reporting to increase robustness and transparency for case series.
Finally, considering that surgical techniques are usually complex, involving many steps and factors that may affect the outcomes of patients, investigators are encouraged to refer to guidelines such as the SUPER guideline83 (surgical technique reporting checklist and standards), valid for case reports, case series, observational studies or randomized controlled trials.

Data reporting

- A predefined target IOP is more appropriate as a clinical trial outcome 'success' measure. Both an upper limit of IOP and a percentage reduction of IOP are recommended
- Survival curves as Kaplan-Meier analysis of time to failure should be considered mandatory in the graphical representation of results. Survival is defined according to the target IOP success criteria
- Scatterplots are particularly helpful
- While postoperative reduction in glaucoma medication gives an estimate of relative efficacy between procedures, its use as a parameter for success is highly susceptible to bias

7. Complications

Current knowledge about complications in glaucoma surgery is derived from case reports, retrospective studies, prospective cohorts, and randomised controlled clinical trials. The most accurate reporting is from prospective studies where protocols define the recording of complications in advance and ensure that comprehensive and consistent reporting is undertaken. In an attempt to standardise and ensure complete and consistent reporting guidance is provided by both the CONSORT[84] and PRISMA[85] consortia.

The importance of consistency in reporting results in glaucoma surgery was demonstrated: changing the criteria for the definition on success significantly affected the success rates in a cohort of patients following trabeculectomy.[86] Applying different distinct definitions of success could result in a difference of nearly 50% in the success in the same cohort of patients, thus clearly emphasising the importance of consistency in the definitions and the component parts used to define a successful outcome.

As mentioned in Chapter 6, the consistency in outcome criteria is relevant.[87-89] Substantial variations in the list of complications, the definitions used to define them and the timings at which the complications are reported were noted.[87-89]

Such inconsistencies make it impossible to effectively compare interventions described in different reports.

The growing number of glaucoma surgery options and the expectations of patients make it imperative that the surgical complications are described consistently and accurately to allow informed treatment choices.

Furthermore, quality of life and the ability to continue to live an independent lifestyle remain the most important outcomes for patients undergoing glaucoma surgery.[90,91] Accurate and comprehensive reporting of potential complications is essential to inform clinicians and patients on the risk of surgery complication and allow valid comparisons among options to allow patients to make informed decisions for their treatment. In addition, not all complications are equal in terms of severity or of consequences for patients, better characterization is therefore required.

7.1 Definition of complications

To be considered a complication of glaucoma surgery, the following conditions must be fulfilled:

- The effect must be consistent with the following literature-based generic definition of surgical complications: “any undesirable, unintended, and direct result of an operation affecting the patient, which would not have occurred had the operation gone as well as would reasonably be expected”.[92]

– The effect must be clear and specific (for example, a generic term such as “infections” would be excluded).

Many complications can arise due to glaucoma surgery.[87,89] These complications can be considered common to all interventions or specific to a particular category of glaucoma surgery. An overview of general and procedure-specific complications of glaucoma surgery was published (Figure 8); this could be adopted for reporting future clinical data (Table 7) to ensure consistency in complication definitions. A complication with the same name can be defined differently by different reports, making comparisons difficult.

The EGS surgery consensus committee has attempted to provide more granular information for several of the complications (Tables 8-12).

7.2 Severity grading

Patients are concerned about the effects of treatments for their glaucoma on their quality of life.[90,93-96] Although providing a comprehensive list of complications is important, not all complications are equivalent, and the severity of complications that may affect quality of life is an important consideration in reporting. There is no standardized way of reporting potential harm to patients and complication discussions typically occur prior to surgery during the consent process and more extensively following surgery if any harm occurs. This issue was addressed in a consensus exercise, to develop a severity grading consensus amongst glaucoma specialists for a limited number of complications.[97] However, further work is required to provide a more comprehensive evaluation of the severity of each condition and develop more patient- friendly metrics for defining severity.

7.3 Timing of harm reporting

Postoperative complications can broadly be considered early or late, but the timing of harm is often not reported. A reasonable approach may be to consider an early complication as one that occurs within 3 months of the operation, a period after which the healing following surgery is normally complete, and late when occurring after 3 months.

7.4 Reporting complications

All surgical trials should be designed to report the safety of interventions, including references to adverse events and those that are “expected” and “unexpected” or “related” and “unrelated” to the interventions being studied, including the description and number of serious vs non-serious complications as determined by the investigators. Such planned reporting should be included in the study protocol before the trial commences.
Table 7 offers a set of definitions that can be adopted for future reports.
Tables 8 to 13 describe templates for reporting complications from glaucoma surgery, which could facilitate consistency. Graphics for reporting harm offer an additional method of representing complications that provide instant visual information about the complication frequency, timing and severity of complications, making this information more easily accessible for clinicians and potentially acting as a useful tool for conveying such information to patients. For the sake of potential comparative studies, we provide surgery- specific complications for most of the traditional surgical comparators. Different methods of Harms Graphics Reporting are included in Table 13.

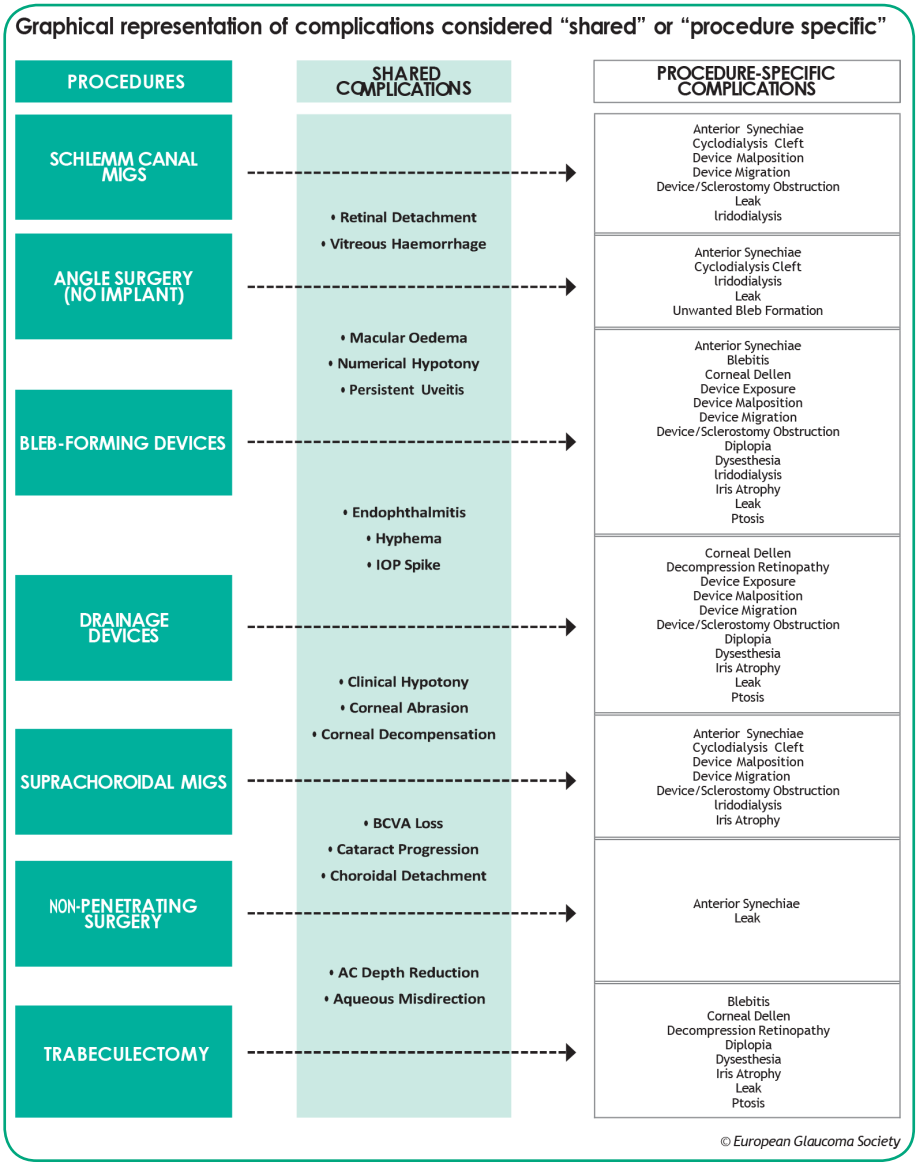


Figure 8 *Procedure-specific categorisation of the final table. The column on the left represents the procedures from the revised trials, grouped according mechanism of action. The middle boxes include the 16 complications that have been found to be in common to all the procedures retrieved from the previously conducted systematic review. The column on the right shows the complications relevant to each procedure: each box is connected to the correspondent procedure by an arrow with dashed line. AC: anterior chamber; IOP: intraocular pressure; MIGS: minimally invasive glaucoma surgery; BCVA: best corrected visual acuity.*

Reproduced from Stringa et al[89]

Table 7. Complication Definition

Complication Name	Revised Definition
Clinical Hypotony	IOP <6 mmHg associated with choroidal detachment and/or with hypotony maculopathy and/or with AC depth reduction. Or IOP < 6 mmHg for which surgery to reverse hypotony-related complications was performed.
Numerical Hypotony	IOP <6 mmHg with no associated complications.
Choroidal Detachment	Any extent of dome-shaped elevations extending posteriorly from the peripheral retina visualised on fundus examination or imaging techniques. Includes choroidal effusion (serous content) and suprachoroidal haemorrhage (blood content).
Mild Anterior Chamber Depth Reduction*	Decreased distance between iris and cornea compared to preoperative depth. Grade 0: AC depth reduction without iris-corneal touch. Grade 1: AC depth reduction with peripheral iris-corneal touch.
Severe Anterior Chamber Depth Reduction*	Decreased distance between iris and cornea compared to preoperative depth. Grade 2: AC depth reduction with complete iris-cornea touch, but no lens-cornea touch. Grade 3: AC depth reduction with lens-cornea apposition.
Leak	Positivity to Seidel test in any location or from the wound edge of a filtering bleb.
Microhyphema*	Blood in the anterior chamber visible by slit lamp. Quantification is advised: Grade 0: RBC circulating in AC.
Visible-hyphema*	Blood in the anterior chamber visible by slit lamp. Quantification is advised: Grade 1: Visible blood level in the AC, but not filling the AC entirely. Grade 2: Blood filling the AC entirely.
Endophthalmitis	Purulent infection involving the vitreous and the aqueous (i.e., cells in the AC and the vitreous).
IOP Spike	Elevation of 10 mmHg from preoperative IOP.
Cataract Progression	Lens opacity causing loss of 10 ETDRS letters or equivalent from baseline or lens opacity requiring surgery.
Corneal Decompensation	Corneal oedema persisting for over 4 weeks following surgery, not responsive to topical treatment.
Persistent Uveitis	Presence of cells (SUN grade > 1+ cell) in the AC, that does not resolve after 6 weeks postoperatively.
Mild BCVA Loss*	Irreversible loss of vision of 5-10 ETDRS letters or equivalent.
Moderate BCVA Loss*	Irreversible loss of vision of 10–20 ETDRS letters or equivalent.
Severe BCVA Loss*	Irreversible loss of vision of 20 or more ETDRS letters or equivalent but not light perception (NLP).
Blinding BCVA Loss*	Irreversible loss of vision to no light perception (NLP).
Device Exposure	Loss of tissue coverage over any part of a glaucoma implant that causes it to be in direct contact with the ocular surface.
Cyclodialisis Cleft	Any extent of separation between the ciliary body and the scleral spur visible on gonioscopy or imaging.

Complication Name	Revised Definition
Ptosis	Clinically significant dropping of the superior eyelid (i.e., interfering with the field of vision or for which surgical correction was performed).
Device/Sclerostomy Obstruction	Clinically visible blockage of an implanted drainage device or of a sclerostomy, regardless of its nature and location.
Blebitis	White bleb containing mucopurulent material surrounded by intense conjunctival injection. AC inflammation can be present, but no vitreous inflammation.
Aqueous Misdirection	Reduced central AC depth due to anterior displacement irido-lenticular diaphragm without choroidal detachment, with elevated or normal IOP and in the absence of pupillary block mechanism.
Macular Oedema	Any amount of intraretinal fluid located in the macular area visible on fundus examination or by imaging techniques.
Retinal Detachment	Separation of the neurosensory retina from the retinal pigment epithelium visible on fundus examination or by imaging techniques.
Device Malposition	Undesired location of a glaucoma implant or part of it relative to its intended position that is not the result of the migration of a previously well positioned implant.
Vitreous Haemorrhage	Blood in the vitreous cavity, noticeable upon clinical examination or imaging techniques.
Diplopia	Double vision in binocular conditions due to misalignment of the eyes in any position of gaze.
Corneal Dellen	Depressed area with sharply defined edges and intact epithelium overlying a thinned area of dehydrated corneal stroma.
Corneal Abrasion	Postoperative corneal epithelial defect visible on slit lamp examination.
Anterior Synechiae	Abnormal adhesions between the peripheral iris and the irido-corneal angle.
Dysesthesia	Any combination of ocular pain, discomfort, burning, foreign body sensation, and tearing that develops or persists after 6 weeks from the surgery date, as reported subjectively by the patient.
Decompression Retinopathy	Retinal haemorrhages following acute lowering of the intraocular pressure.
Device Migration	Undesired location of a glaucoma device or part of it relative to its intended position resulting from a postoperative shift in its original positioning.
Unwanted Bleb Formation	Undesired subconjunctival aqueous drainage following nonpenetrating surgery.
Iris Atrophy	Iris atrophy causing vision disturbance.
Iridodialysis	Localized separation or tearing away of the iris from its attachment to the ciliary body.

** Modified from Stringa's original table[87]*

Table 8 Proposed complication reporting tables

Complication Name	Early [N (%)]	Late [N (%)]
Clinical Hypotony		
Numerical Hypotony		
Choroidal Detachment		
Mild Anterior Chamber Depth Reduction		
Severe Anterior Chamber Depth Reduction		
Micro Hyphema		
Visible Hyphema		
Endophthalmitis		
IOP Spike		
Cataract progression		
Corneal Decompensation		
Persistent Uveitis		
Mild BCVA Loss		
Moderate BCVA Loss		
Severe BCVA Loss		
Blinding BCVA Loss		
Aqueous Misdirection		
Macular Oedema		
Retinal Detachment		
Vitreous Haemorrhage		
Corneal Abrasion		

N = number of participants with complications

Table 9 Subconjunctival bleb-forming device complications

Complication Name	Early [N (%)]	Late [N (%)]
Anterior Synechiae		
Blebitis		
Leak		
Ptosis		
Diplopia		
Corneal Dellen		
Dysesthesia		
Decompression Retinopathy		
Iris Atrophy		
Iridodialysis		
Device/Sclerostomy Obstruction		
Device Malposition		
Device Migration		
Device Exposure		

N = number of participants with complications

Table 10 Trabecular surgery

Complication Name	Early [N (%)]	Late [N (%)]
Stenting with implant MIGS complications		
Leak		
Anterior Synechiae		
Cyclodialysis Cleft		
Device/Sclerostomy Obstruction		
Device Malposition		
Device Migration		
Iridodialysis		
Disruptive and Dilating (no implant) MIGS complications		
Leak		
Anterior Synechiae		
Cyclodialysis Cleft		
Unwanted Bleb Formation		
Iridodialysis		

N = number of participants with complications

Table 11 Nonpenetrating surgery and Trabeculectomy complications

Complication Name	Early [N (%)]	Late [N (%)]
Nonpenetrating surgery		
Anterior Synechiae		
Leak		
Trabeculectomy		
Leak		
Ptosis		
Blebitis		
Diplopia		
Corneal Dellen		
Dysesthesia		
Decompression Retinopathy		
Iris Atrophy		

N = number of participants with complications

Table 12 Glaucoma drainage device complications

Complication Name	Early [N (%)]	Late [N (%)]
Leak		
Ptosis		
Diplopia		
Corneal Dellen		
Dysesthesia		
Iridodialysis		
Iris Atrophy		
Device/Sclerostomy Obstruction		
Device Malposition		
Device Migration		
Device Exposure		

N = number of participants with complications

Table 13 Summary of graphic format to display complications collected in trials

Visualization	Data format for creation	Characteristics presented	Pros	Cons
Bar Chart Unique harms are arranged along x-axis in an order of the authors' choice (e.g., descending or ascending effect size, alphabetical).	Aggregate data	• Occurrence of each harm by trial arm (y-axis) • Distribution of severity for each harm (colour distribution in each bar)	• Easy to understand • Moderate value for communicating harms as rated by experts	• Figure becomes wide with many events (each unique harm gets a column) • Limited information presented
Dot Plot Unique harms are arranged along the y-axis in an order of the authors' choice.	Aggregate data	• Comparative measure of effect (x-axis on the right panel of the figure) • Uncertainty (95% CI around points on the right panel of the figure) • Incidence/occurrence of each harm by trial arm (x-axis on the left panel of the figure) Note: Additional "panels" of information can be added to present data on other characteristics (e.g., the distribution of severity ratings for each unique harm)	• Easy to understand • Expandable format using a panel approach • High value for communicating harms as rated by experts	• Figure becomes long with many events (each unique harm gets a row)
Heatmap Unique harms are arranged along the y-axis in an order of the authors' choice.	Aggregate data	• Standardized comparative measure of effect (colour) • Subgroups of participants experiencing each harm (x-axis) Note: Choose whichever subgroups are desired for exploration (e.g., male/female, young/old, low/high dose, severe/not-severe, etc.) and restrict to events in that subgroup before calculating the standardized measure of effect.	• Allows exploration of harms within and across subgroups • Moderate value for communicating harms as rated by experts	• Difficult to understand • Figure becomes long with many events (each unique harm gets a row) • Overwhelming with too many events and subgroups

Visualization	Data format for creation	Characteristics presented	Pros	Cons
Volcano Plot Unique harms are represented by bubbles placed on an X-Y grid.	Aggregate data	• Comparative measure of effect (x-axis) • Overall occurrence of each harm (size of bubble) • P value (y-axis and opacity of bubble) • Trial arm positively associated with each harm (colour) Note: 'Colour' and 'opacity' of bubbles could be used to represent other dimensions (e.g., seriousness or whether the harms are recurrent) as their characteristics are already represented by the harms' positions on the x and y-axis, respectively.	• Can present up to five dimensions of data in a relatively condensed space • High value for communicating harms as rated by experts	• Events with the same data (i.e., counts in each arm) will occupy the same space
Tendril Plot Unique harms are represented by distinct tendrils which are created by adding vectors created by the connection of two instances/events for a unique harm in a coordinate space.	Individual participant data	• Overall occurrence of each harm (size of each harm's points) • P value (colour of each harm's points) • Duration between each event (length of each vector) • Trial arm that had the event (direction of the vector)	• Detailed visual for the timing of every event allows users to see which harms occur more often soon after exposure and which occur later or equally over time. • More useful for a few unique harms of interest	• Very difficult to understand • Low value for communicating many harms as rated by experts

8. Outcomes for clinical trials

8.1 The problem of outcome multiplicity

An outcome is a measure or event used to assess the effects of interventions.[98] In clinical trials, the effectiveness and harms of an intervention are assessed by comparing the outcomes of the participants in the intervention group with those of the patients in the comparison group.

The efficacy of clinical trials in informing clinical practice is dependent on the possibility to report outcomes that are relevant and important to key stakeholders; including patients, health care professionals and anyone making decisions about health care.[99] When various clinical trials on a topic report different outcomes, it becomes a challenge to meaningfully compare results because of the lack of common benchmarks. Such heterogeneity in outcome reporting has been demonstrated across a wide range of health conditions and healthcare interventions. As many as 40% of recent Cochrane systematic reviews of various topics identified outcome heterogeneity across included clinical trials as a problem for the synthesis.[100] Such heterogeneity has also been well documented within ophthalmology.

8.2 What are core outcome sets?

A core outcome set (COS) is an important aspect of the solution for outcome heterogeneity. A COS is an agreed standardized set of outcomes that should be measured and reported, as a minimum, in all clinical trials in specific areas of health or health care.[99]

Once a COS is developed, it is expected that the outcomes in it will always be reported by trials. However, researchers working on a particular trial will likely also be interested in other outcomes of relevance to that trial. Because a COS is a minimum set, its use does not preclude researchers from measuring and reporting any additional outcome of interest.[101]

8.3 Core outcome set development

8.3.1 Stakeholder involvement

COSs are intended to be developed using methods that incorporate various stakeholder preferences for which outcomes should be considered "core". According to the handbook for COS development, stakeholders should include healthcare practitioners, trialists, regulators, industry representatives, policymakers, researchers, patients, other health service users and the public.[101,102]

8.3.2 Steps of core outcome set development

COSs are generally determined by an initial systematic review to identify all potential outcomes followed by a process to prioritize the most important outcomes based on consensus among the participating stakeholders.[101] The initial focus is on developing a consensus on what to measure, i.e., the outcomes in the COS. For some COSs, an additional step is taken to develop a consensus regarding the instruments used for measuring the outcomes. Consensus is usually developed using formal methods, such as the Delphi method involving multiple rounds of iterative discussions and consensus generation.[101]

8.3.3 COMET database and core outcome sets in Ophthalmology

The Core Outcome Measures for Effectiveness Trials (COMET) Initiative is an international effort that brings together people and groups interested in the development and application of COSs. The initiative's aims are to collate and stimulate relevant resources to facilitate the exchange of ideas and information and to foster methodological research in this area.101 The Initiative maintains the COMET Database – a free, publicly available database of published and ongoing COSs (available at www.comet-initiative.org).[103] There is some variability across fields in the number of COSs developed.[103] Unfortunately, ophthalmology has a low number of COSs (three – geographic atrophy and age-related macular degeneration and glaucoma[104-106]), neither of which is specific for glaucoma.

8.3.4 Advantages of core outcome sets

There are two main reasons why COSs have been developed. Firstly, they help ensure that key stakeholders can inform the set of outcomes to measure in clinical trials for a given health condition. Secondly, the results of such trials having reported at least the COS in common, can be incorporated into systematic reviews and meta-analyses to inform regulatory and healthcare guidance and decision making.[100,107-109] COS use is increasingly endorsed by a broad set of stakeholders in the evidence ecosystem. These include trialists, trial funders, trial registries, regulatory authorities, systematic review groups, clinical practice guideline developers and journal editors (see www.comet-initiative.org/COSEndorsement).

8.3.5 Summary

In summary, COSs can serve an important purpose in addressing the problem of outcome heterogeneity across clinical trials. More COS researchers and various relevant stakeholders should participate to or lead the development of COSs. The ultimate goal is for COSs to improve health by facilitating more impactful clinical trials, more reliable systematic reviews, more informed clinical practice guidelines leading to more informed health decisions and improved health.

8.4 Outcomes and descriptors for glaucoma studies evaluating surgical innovations

In recent years, we have seen an increasing number of trials investigating the benefits and harms of surgical innovations in glaucoma. However, as pointed out in the previous chapter, no COS has been defined for trials evaluating novel surgical interventions for glaucoma. Thus, outcome reporting varies widely, and the consequence is that RCT evidence may be less useful than expected because of the variation in currently reported outcomes and the inability to compare different interventions. Therefore, a COS is advocated to ensure that critically important outcomes are consistently reported in all clinical studies investigating surgical innovations in glaucoma.

To solve this unmet need, EGS has worked with numerous experienced glaucoma surgeons to develop a COS for innovative glaucoma surgeries and to agree on a number of descriptors and other aspects that will be useful in the design and conduct of trials.

This includes suggestions for developing a clinical research form (CRF) for data collection. Future work will be needed to involve patients and other relevant stakeholders.

8.4.1 Methology

A 3-step process was undertaken: 1) the identification of reported outcomes and descriptor measures of glaucoma trials evaluating surgical innovations from published clinical studies and systematic reviews, 2) a grading system for the relevance of the reported outcomes and descriptors by experts through an electronic survey, and 3) consensus among experts after two face-to-face meetings.
In this process, a distinction is made between early-phase (exploratory and efficacy studies, IDEAL phase 2) and late-phase (i.e., definitive effectiveness studies, IDEAL phase 3) trials (see Table 6).
Each proposed outcome or descriptor is labelled “Highly Recommended” or “Optional”.

- “Descriptors” were grouped into 3 domains: Population, Surgical Procedure, Follow-up time,
- “Outcomes” were grouped into several domains: (i) clinical effectiveness, including IOP lowering efficacy, additional postoperative interventions for glaucoma, visual function, and structural evaluations with OCT; (ii) quality of life (QoL) and patient-reported outcome measures (PROM) and (iii) safety,
- “Analysis” was grouped into 4 domains: Descriptive statistics, Charts, Methods, and Reporting.

Table 14

DESCRIPTORS

Population	Highly Recommend	Optional
Age	X	
Sex	X	
Ethnicity	X	
Systemic/ocular comorbidities	X	
Type of Glaucoma	X	
Medicated preoperative IOP	X	
Unmedicated preoperative IOP (washout)		X
Mean/median number of preoperative medications	X	
Mean deviation/mean defect	X	
Lens status (phakic, pseudo, aphakia)	X	
Number and type of previous ocular surgeries/laser	X	
BCVA (LogMAR)	X	
CCT		X
Average RNFL/GCC thickness		X
Baseline mean/median endothelial cells count	X	

Table 14 Part 2

SURGICAL PROCEDURE

Population	Highly Recommend	Optional
Surgeon experience (#cases of the technique/s under investigation)	X	
Use of Antimetabolites	X	
Type	X	
Concentration	X	
Mode of application	X	
Time of application	X	

FOLLOW-UP TIME POINTS

Population	Highly Recommend	Optional
1 day *		X
1 week	X	
1 month	X	
3 months	X	
6 months	X	
12 months	X	
Every 6 months for follow up > 12 months	X	

Notes
* *Recommended for surgical techniques in their early stage of development*

Table 14 Part 3

OUTCOMES

Efficacy	Highly Recommend	Optional
IOP		
Mean/median absolute postoperative IOP	X	
Mean/median postoperative IOP change	X	
Mean/median % postoperative IOP change	X	
Proportion of patients at postop IOP levels:	X	
≤21 mmHg	X	
≤18 mmHg	X	
≤15 mmHg	X	
≤12 mmHg	X	
Ocular hypotensive medications		
Mean/median number of post operative medications	X	
Number (and %) of patients by number of hypotensive medications (0,1,2,3,4, +)	X	
Mean/median N of medication change from baseline		X
Post-operative interventions		
Number for each intervention	X	
Number (and %) of patients requiring 0, 1, 2, or more interventions	X	
Visual function		
Mean postoperative Mean deviation/Mean defect	X	
Pre and post operative RoP **		X
OCT derived structural measures		
Average RNFL/GCC thickness		X

Table 14 Part 4

SAFETY

Efficacy	Highly Recommend	Optional
Complications		
Number (and %) of each complication	X	
Number (and %) of patients with 0, 1, 2, or more complications	X	
Intraoperative complications	X	
Postoperative complications	X	
Early complications (<1 month)	X	
Late complications (≥3 month)	X	
Serious complications (sight threatening)	X	
Not serious complications (not sight threatening)	X	
Endothelial corneal cells		
Mean/median absolute ECC	X	
Mean absolute change of ECC		X
Mean % reduction of ECC	X	
Number (and %) of patients showing an ECC loss >20,>30,>40%	X	
Visual acuity		
BCVA (LogMAR) mean/median	X	
BCVA (LogMAR) mean/median change	X	
N(%) of patient by # of lines lost	X	
QOL		
NEI-VFQ-25, 15D, SF-5, EQ-5D		X

Notes
*** Recommended only for studies longer than 2 years. RoP: Rate of progression.*

Table 14 Part 5

METHODS OF ANALYSIS AND REPORTING

Descriptive statistics	Highly Recommend	Optional
Mean/median and dispersion measures for all continuous variables	X	
Definition of MCID	X	
Sample size calculation	X	
Definition of criteria used for reintroducing hypotensive medications during the follow-up	X	
Kaplan Meier curves	X	
≤21 mmHg	X	
≤18 mmHg	X	
≤15 mmHg	X	
≤12 mmHg	X	
Intent to treat Analysis	X	
Per protocol Analysis	X	
# of patients analyzed at each time-point for each outcome	X	
Charts		
Scatterplot (Baseline vs Follow-up IOP, by # of meds with % reductions and absolute reduction threshold lines)	X	
Standards for reporting		
CONSORT for RCTs (IDEAL and PROCESS guidelines may be considered as appropriate for studies different from RCTs)	X	

8.4.2 Descriptors

8.4.2.1 Population

A detailed description of the characteristics of the study population is essential in any clinical study, including those on surgical innovations in glaucoma. Recommended population descriptors include demographics, health status, ocular characteristics, lens status, comorbidities and previous interventions, as well as glaucoma-related structural and functional parameters. Details about these descriptors can be found in Table 14.
Three descriptors

- unmedicated preoperative IOP after washout
- CCT
- OCT derived structural measures

were labelled optional as discussed in Chapter 6.

8.4.2.2 Surgical procedures

Surgical procedures are complex interventions in which skills can influence outcomes. Surgeon experience in the technique(s) being evaluated (e.g., number of previous surgeries) has therefore been labelled as a "highly recommended" descriptor. Due to the different complexities and stages of innovation of surgical techniques, the length of the learning curve may differ widely. The lack of more standardized ways of measuring the learning curve necessitates reporting the number of surgical procedures performed by the treating surgeon(s) as the best available surrogate of surgeon experience.

8.4.2.3 Use of antimetabolites in bleb-forming techniques

The use of antifibrotic agents can significantly impact the outcomes of glaucoma filtering surgery, and their use should be reported and detailed in any related clinical study, including the type (i.e., MMC, 5FU, topical steroids), dose (e.g., concentration, volume, time of exposure), and mode of application (i.e., sponges, subconjunctival injection).

8.4.2.4 Follow-up time points

Early surgical trials evaluating the short-term efficacy of innovative techniques may not report long-term follow-up to be clinically relevant. However, the timing and frequency of follow-up visits is relevant for an accurate and timely assessment of any outcome, including safety considerations. The frequency of testing should be adjusted according to the type of outcome, to the likelihood of occurrence of a relevant change in each timeframe and to the time from the operation. For most safety and efficacy outcomes, a minimum set of highly recommended postoperative time points has been identified: 1 week, 1 month and 3-6-12 months. For studies longer than 12 months, a follow-up visit may be scheduled every 6 months.

As mentioned above, the follow-up time point of Day 1 has been labelled as "highly recommended" only for studies involving surgical techniques in their early stage of development, where limited knowledge is available about the very early postoperative period.

Recommended Descriptor Reporting

- Demographic, health status, ocular co-morbidities and glaucoma related structural and functional parameters
- Number of surgical procedures performed by the treating surgeon(s) as the best available surrogate of surgeon experience
- Type, dose and application mode of cytotoxic agent (if applicable)
- Safety and efficacy outcomes reported at Week 1, Month 1, Month 3, Month 6 and Month 12 timepoints

8.4.3 Outcomes

8.4.3.1 Efficacy

8.4.3.1.1 IOP

IOP is typically considered the primary outcome in trials evaluating novel surgical interventions. A clear and standardized definition is of critical importance.
It is mandatory to report IOP as the mean value, including the absolute (mmHg) and relative (%) change from baseline, with an appropriate measure of data dispersion (e.g., standard deviation).
Additionally, it is valuable to report the proportion of patients showing an IOP below predefined thresholds (<21, <18, <15, <12 mmHg) to better describe the distribution of IOP at follow-up.
All possible efforts to mask investigators measuring IOP should be made. When slit-lamp tonometry risks the possibility of identifying the intervention, steps should be taken to avoid bias, including for example measurements being performed by an external observer or a two-observer technique. The choice of alternative tonometers other than GAT may limit the ability to compare between studies. (see also Chapter 6)

8.4.3.1.2 Ocular hypotensive medications

The use of hypotensive medications during follow-up, if not adequately standardized per protocol according to predefined criteria, might introduce significant bias both in the estimation of efficacy and in the comparability between different surgical interventions.
Although the definition of these criteria may vary from trial to trial due to numerous factors, authors are required to clearly report the criteria used for the reintroduction and the step-up of ocular hypotensive therapy, topical and systemic.

The mean/SD number of topical hypotensive medications (active principles) and the number and percentage of patients who are medicated or not must be reported at each study time point. (see also Chapter 6.6.4)

8.4.3.1.3 Postoperative interventions

The number of additional interventions for IOP control and those required to manage complications must be reported. Interventions for IOP control include needling, suture lysis or removal, surgical revision, and additional glaucoma surgery.
Since more than one intervention may be required for the same patient, reporting the number and % of patients requiring 0, 1, 2 or more postoperative interventions is also highly recommended, (see also Chapter 6.1.5).

Recommended Efficacy reporting

- IOP as the mean value, including the absolute (mmHg) and relative (%) change from baseline
- Criteria for the reintroduction and the step-up of ocular hypotensive therapy (topical and systemic)
- Interventions for IOP control, which include needling, suture lysis or removal, surgical revision, and additional glaucoma surgery

8.4.3.1.4 Perimetry

Visual function, as assessed by standard automated perimetry, is an important outcome for any surgical intervention for glaucoma both from the efficacy and safety points of view.
Evaluating differences in disease progression between interventions is essential to assess the long-term effectiveness of glaucoma treatment, in general. However, trials to evaluate surgical innovations may not always require long-term follow-up and assessment of disease progression. When visual field outcomes are considered, the mean and SD of perimetric indexes (mean deviation or mean defect) are highly recommended outcomes and should be assessed and reported at appropriate time points during follow-up.
The assessment of the rate of progression of visual field damage requires more frequent testing or a longer follow-up to be accurate; therefore, these assessments are considered "highly recommended" only for studies exceeding 2 years. (see also 6.3)
Severe visual field loss may be considered among complications.

8.4.3.1.5 Optical Coherence Tomography

Structural measures like Optical Coherence Tomography (OCT), can be useful in glaucoma surgical trials and were labelled "optional". (see also 6.4)

8.4.3.2 Safety

Please see Chapter 7 for an overview of postoperative complications. The number and % of each complication should be reported, and this reporting is considered highly recommended. Since more than one complication may be present in the same patient, reporting the number and % of patients with 0, 1, 2 or more postoperative complications is also considered highly recommended.
Complications need to be reported threefold: 1) as intraoperative or postoperative, 2) as early or late complications, occurring before or after 3 months from the operation and 3) as serious, sight threatening or nonserious.
The occurrence of low IOP measurements (lower than 6 mmHg) is a common finding after many glaucoma surgical procedures and should be reported. Only if symptomatic should it be labelled clinically relevant hypotony and reported as an adverse event.

8.4.3.2.1 Endothelial corneal cells

Endothelial corneal cells (ECCs) might be damaged by ocular surgery, and the mean/ median absolute ECC count and mean % reduction from baseline must be reported as a "highly recommended" safety measure.
The mean/median absolute change in endothelial cell count from baseline has been labelled an optional outcome since it can be calculated from the baseline count and % reduction at follow-up.
Additionally, the number and % of patients showing an ECC reduction greater than 20, 30, and 40% from baseline must be reported to better describe the distribution of ECC loss in the study population.

8.4.3.2.2 Visual acuity

Best corrected visual acuity is considered a highly recommended outcome, particularly as a safety measure. The methodology for correct measurement and reporting of BCVA is described in Chapter 6.2.

Recommended Safety Reporting

- Number and % of each complication
- Number and % of patients with 0, 1, 2 or more postoperative complications
- The mean/median absolute ECC count and mean % reduction from baseline
- Best corrected visual acuity

8.4.3.3 Quality of Life

The ultimate goal of healthcare is to maintain or improve QoL. In addition to traditional clinical endpoints health-related QoL outcomes and, more broadly, patient-related outcomes are important additional parameters to consider when evaluating the quality or success of an intervention (see also Chapter 6.5).

Several QoL questionnaires are available for glaucoma. There is no reference standard to assess patient-related outcome measures in glaucoma. Investigators rely upon questionnaires that measure the impact of the disease, treatment effect, symptoms, side effects, daily activities or general well-being one time point or longitudinally in the most appropriate manner for the evaluated surgical procedure. Additionally, investigators must consider that the correlation between glaucoma severity grade and QoL questionnaire scores is not linear, and some questionnaires may have a ceiling effect when used at the earliest stage of the disease.

Questionnaires in this field are particularly challenging for several reasons: 1) Vision Related (VR) QoL questionnaire results are not affected until more advanced stages of glaucoma
2) the questionnaires may not be sufficiently sensitive to detect change as the results are not impacted even in the presence of visual field progression small magnitude 3) in surgical trials it is reasonable to expect some adverse effect on QoL immediately after surgery, and possible benefits may take a long time to appear. This issue is even more critical if the two study arms are not entirely similar in terms of invasiveness (i.e., VS cataract surgery alone or VS medication).

Furthermore, it has been reported that currently available instruments might not be sufficiently sensitive to detect differences secondary to different interventions.

Various questionnaires have been developed; some are highly specific to symptoms associated with a disease (glaucoma-specific questionnaires), while others are designed to measure vision-related quality of life. Finally, some generic questionnaires aim to capture broader aspects of general health.

This issue is further expanded in Chapter 6

Table 15 summarizes the main features of the questionnaires.

Recommended Quality of life Reporting

- There is no widely accepted instrument to assess patient-related outcome measures to evaluate interventions in glaucoma
- Currently available instruments might not be sufficiently sensitive to detect differences secondary to different interventions

Table 15 The following table summarises some of the questionnaires used for glaucoma patients. In this context, although the assessment of QoL is welcome in a glaucoma surgical trial, its presence in the COS is considered optional. Examples of instruments used for these assessments include the NEI-VFQ-25 and/or the 15-D, EQ-5D, and SF6D questionnaires.

Patient-Related Outcome Measures (PROM) instruments		Number of Domains- Items	Domains-Items	Comments
Generic instruments	EuroQOL's 5 dimensions 5 levels (EQ-5D-5L)	5 domains/5 levels of responses	• Mobility • Self-care • Usual activities • Pain/discomfort • Anxiety/Depression	• Assessment of QALYs/ Cost-utility & Cost-effectiveness analyses • 3,125 possible health states
	Health Utility Index mark 3 (HUI-3)	8 domains/6 levels of responses	• Vision • Hearing • Speech • Ambulation • Dexterity • Emotion • Cognition • Pain	• Assessment of QALYs/ Cost- utility & Cost- effectiveness analyses • 972,000 possible health states
	Short Form- 6 dimensions (SF-6D)	6 domains/4 to 6 levels of responses	• Physical function • Role limitation • Social function • Body pain • Mental Health • Vitality	• Assessment of QALYs/ Cost- utility & Cost- effectiveness analyses • 18,000 possible health states
Vision-related instruments	National Eye Institute visual functionning questionnaire (NEI-VFQ-25)	25 questions/12 subscales items	12 subscales items: General Health/General vision/ Near vision/Distance vision/Driving/ Peripheral vision/Colour vision/Ocular pain/Vision specific (Role limitation, dependency, social function, mental health, expectations for future vision)	• Provides information about general consequences of visual impairment
	Impact of Vision Impairment (IVI)	28 items/3 subscales items	3 subscales items: Reading and accessing information/ Mobility and Independence/ Emotional Wellbeing	

Patient-Related Outcome Measures (PROM) instruments		Number of Domains- Items	Domains-Items	Comments
Glaucoma-related instruments	Treatment Satisfaction Survey Intraocular Pressure (TSS-IOP)	5 items	Effectiveness/side effects/ eye appearance/convenience of use/ease of administration	• Items more specific to medical treatment
	Glaucoma Symptom Scale (GSS)	10 items	Burning/tearing/dryness/ itching/ soreness/blurry/feeling of something in the eye/ hard to see in day light/hard to see in dark places/ halos around lights	• Items more specific to medical treatment
	Glaucoma Quality of Life-36 (Glau- Qol 36)	36 items grouped into 7 subscales	Psychological wellbeing (6 items)/ Self-image (5 items)/Daily life (9 items)/ Burden of treatment (5 items)/Driving (3 items)/Anxiety (4 items)/ Confidence in health care (4 items)	
	Glaucoma Quality of Life-15 (GQL-15)	15 vision-related items grouped into 4 subscales	Central and near vision (2 items)/ peripheral vision (6 items)/Dark adaptation and glare (6 items)/ outdoor mobility (1 item)	
	Glaucoma Activity Limitation 9 (GAL-9)	9 items	Walking after dark/seeing at night/walking on uneven ground/ adjusting to dim lights/going from light to dark room and vice-versa/ seeing object coming from the side/ walking on steps, stairs/ judging distance of foot to step-curb/ finding dropped objects.	

Epilogue

By George L. Spaeth, MD

Why do we innovate? Of course, for different reasons. One of them is the awareness that we are not doing as well as we hope to do; another reason, more disturbing, that we are not doing as well as we could do; and yet another, even more troubling, that we are not doing as well as we should do. But where do we want to be? We are unlikely to get to where we want to go if we don't know where that is.

Several thoughts come to mind:

1. *"There" needs to be clearly defined;*
2. *We may be able to get to that place;*
3. *Even if we get "there," it is never the final "perfect" place;*
4. *We shall never get close to "there" unless we travel towards that destination;*
5. *What is a proper way to travel?*

1) "There" needs to be clearly defined

By "there", I mean a place where:

a) *the patient knows his or her concerns, hopes and expectations and is honest and open with both him or herself and the physician,*

b) *the physician understands who the patient is and what that often-fearful person hopes for and needs ("needs" being an amalgam of what the patient and the doctor believe, and is always uncertain). As this destination is unique to each individual, no algorithm will find it. Furthermore, the doctor may believe that the patient's hopes may be unreachable. Therefore, the doctor must be sure that the patient has a realistic understanding; at least, realistic from the doctor's perspective. Ticking off the litany of possible complications and outcomes, as if reading a list of philosopher's names, has become, unfortunately, routine and almost meaningless. More important is for the patient to be able to envision clearly what "there" is likely to look like and to understand with clarity*

that "likely" has a different meaning from "certainly." The surgeon and the patient then conjointly decide what "there" can look like.

2) We may be able to get to that place

The surgeon, during this discussion, must be mentally drawing the road map leading to "there." For example, let us consider that the patient wants to preserve some useful vision so as not to be dependent. There are no other major hopes. The surgeon must then consider the most likely reasons why the patient may lose so much vision as to become dependent and what approach is most likely to be safest. The essentials that will establish the need for treatment and the type of appropriate treatment include the following:

i) **the stage of the condition:** *Green - no symptoms and no finding indicating with near-certainty that the person is likely to develop symptoms, Yellow - no symptoms but a finding indicating the person is almost certain to develop troublesome symptoms, or Red, troublesome symptoms already present;*

i) **the rate of change of the condition;**

i) **the duration the change will continue** *(often an estimate of the number of years prior to the patient's death);*

i) the **likely responses of the patient and the patient's condition** *(they are not the same) to an intervention - for example, cure, reverse problems partly or not at all, and affect the patient's quality of life;*

i) the **socioeconomic circumstances** *that impact the situation. These circumstances not only involve the patient but also require the surgeon to honestly assess his or her skills, learning ability, and support facilities.*

3) Even if we get there, it is never the final "perfect" place

Having defined "there" to the satisfaction of the patient and the doctor, the doctor reminds him or herself that nothing is ever truly stable or unchanging and that the "destination" is just a station on the way to the next stop. In addition, she makes sure that fact is understood by the patient.

(As a momentary but essential digression - that word "understood" jolted me to remind myself and everybody that, after an explanation, even one that seems crystal clear, the person explaining should never ask, while looking earnestly directly at the other person, "Did you understand that?" What can the other person say, smiling agreeably, except "Oh yes," even though, from that person's point of view, the person explaining might as well have been speaking in Esperanto. The proper comment is something like "I don't always explain clearly. What did you understand?").

On further consideration, the surgeon may think, "This man is frail. Though he's only 60, he looks and acts more like a 90-year-old. He is quite comfortable with his present vision. His field has definitely worsened in his only seeing right eye, but the rate of change is truly slow. His life is sedentary, and safety is the highest priority. He probably has only a few years to live, based on his general health. I was thinking of doing a relatively new procedure that I have used in situations like this, because I have not had a serious complication with it, and some doctors call it 'safe,' but every surgical procedure carries some risk." The surgeon should also be very clear in his own mind that the patient will almost certainly accept his recommendation. He says, "Thanks for being so clear with me. A reasonable next step is to keep going just as we are. What do you think about this plan? You come back to see me again in 3 months. Now if you notice a change before then call me right away." The surgeon then sensitively assesses the old man's response to that.

4) We shall never get close to there unless we travel towards that destination

Let's change the details. The patient is a very healthy 52-year-old bank executive. She is terribly worried because her mother lost "all her sight" from glaucoma, and she thinks she is following the same track. Indeed, no treatments thus far have stabilized her. The surgeon is convinced that she needs some type of filtering procedure to get the pressure truly low in the presence of a bleb. However, the patient is a high myope, has far advanced field loss in both eyes extending close to fixation, the sclera flap of a trabeculectomy will be difficult to close because of the thin sclera, and she (the surgeon) is truly worried about causing "wipeout" or causing macular oedema due to an eye that is too soft. BUT, the surgeon knows of a type of tissue glue that was developed by a plastic surgeon. The bond of the glue can be dissolved by exposure to ultraviolet light. Why not suggest to her patient an untried surgical procedure? She had thought of the method a year before and had been trying it in rabbits. The glue worked to prevent filtration. It appeared not to have harmful effects on the rabbit eyes. So why not do her usual type of trabeculectomy with releasable sutures on the banker and cover most of the scleral flap incision with this glue? She could then dissolve the glue in a localized area to allow just a trickle of outflow and only release the releasable sutures if the pressure was not low enough. She had already spoken to the plastic surgeon who developed the product, and she had learned that extensive studies had shown the glue to be noninflammatory and, when dissolved, to be rapidly decomposed by epithelial

tissue. She presents to the patient the possibility of doing this new surgery. She makes clear to the middle-aged woman that this substance has not previously been used in human eye surgery, so she cannot assure the bank executive that it will work and cannot even assure her that it may not be harmful. The surgeon tells the patient, "I do not know whether this will work. I am eager to try this procedure, and I know that biases me. I may be presenting it to you in a more favourable light than is fair to you, but I think it makes sense to try the new operation." The surgeon then lists the options, including the following: 1) no surgery, 2) her version of the standard trabeculectomy with releasable sutures that she explained to the banker, 3) a bleb forming device, or 4) referring the patent to Dr.....in.....for his opinion.
The banker chooses to be referred. If at that point the surgeon is truly disappointed that the patient opts for a referral, the surgeon should recognize that her biases made her too eager to perform the unproven procedure. She should be aware that her sentence, " I think it makes sense to try the procedure" puts the patient in a difficult position. If the patient considers that untested operation unwise, and does not want it performed on her, she will need to say she does not want that operation done on her. For her to say that, however, demands a level of self-confidence and courage that few patients possess; she will need to disagree with her surgeon's recommendation. In cultures still characterized by "the physician knows best" mentality, it is unreasonable to expect a person, even a woman who has become a powerful banker, to disagree with her doctor. The surgeon should not have said "it makes sense to try the procedure." If a surgeon is truly disappointed when a patient chooses something different from what the surgeon recommended, either the surgeon has not explained her choice well, or the surgeon values her own choice more than that of the patient - or has both explained poorly and does not respect the patient's autonomy. In such a situation the surgeon should think more deeply about the doctor-patient relationship, and much more deeply about her blindness to her own biases. On the other hand, if, after the patient opts for a referral, the surgeon genuinely thanks the banker (the patient) for making a good decision, then the surgeon is probably acting as a fine physician, genuinely encouraging a patient to be courageously autonomous.

5) What is a proper way to travel?

In the example given, the surgeon is to be congratulated for wanting to make things **better and acting in a way to try to make that happen. Only by trying to make the world better is it likely to become better.**

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